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Post-Polymerisation Functionalisation of Polyethers by Olefin Cross Metathesis

Stephen Morrison

Master of Sciences – Medicinal Chemistry

Thesis submitted in fulfilment of the requirements for the degree
of Doctor of Philosophy



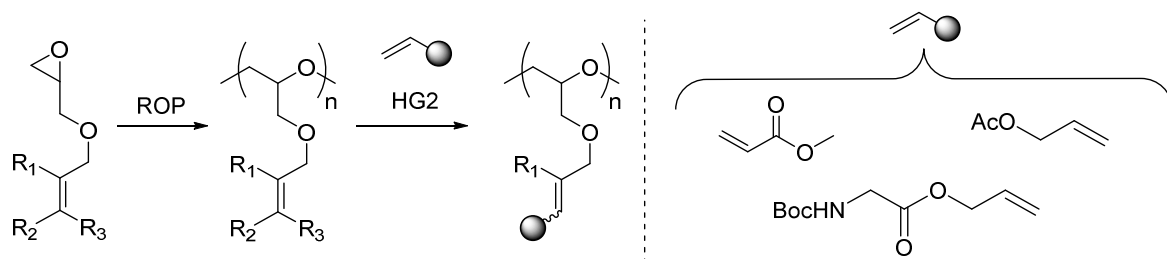
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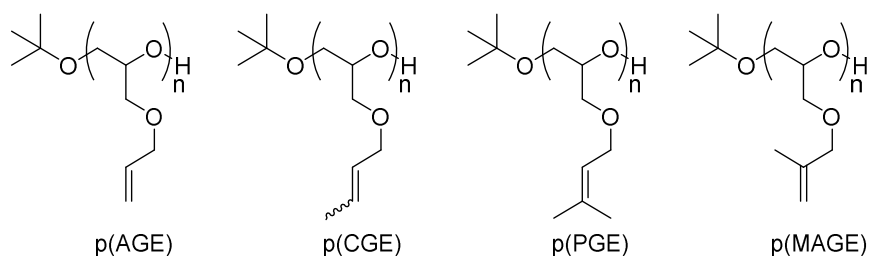
September 2017

Abstract

Industrial uses of polyethers have expanded to medical applications, ranging from artificial tissues (i.e. implants, sutures and prosthetics), to the encapsulation of drugs; however post-polymerisation functionalisation methods are limited. Olefin cross metathesis (CM) is a powerful carbon-carbon bond forming reaction, and therefore could potentially conjugate polymers possessing pendent olefin handles. This could be of significant importance as the alkenes do not readily interfere with common polymerisation techniques such as anionic ring opening polymerisation (ROP), polyesterifications, or polyamidations.



This project describes the synthesis of novel biocompatible polyethers with diverse pendent olefins and their cross metathesis reaction with a range of partners. These various polymers are designed to probe the possibility of preventing the occurrence of self metathesis upon functionalisation using Hoveyda-Grubbs' second-generation catalyst. One such polymer, poly(methallyl glycidyl ether) has been proven to be immune to the undesired self metathesis pathway allowing for retention of the low polymer dispersity ($\mathcal{D} = 1.15$). We have shown that the cell signalling peptide RGD can be coupled efficiently to this polymer.



Author's declaration

This thesis represents the original work of Stephen Morrison unless otherwise explicitly stated and referenced in the text. The research was carried out at the University of Glasgow in the Raphael Laboratory under the supervision of Dr Joëlle Prunet and Prof Rob Liskamp during the period from the 1st of October 2013 to 31st of March 2017.

*A PhD can be lonely
Working ^{late} beneath the lamp,
Fortunately I had two guides
Called Prunet and Liskamp*

*Never a day was had
Where I was made to feel alone,
You both devoted time for me
To listen to me groan*

*So thank you to you both
You have each taught me so much,
Chemistry makes sense now
It's no longer Double-Dutch.*

*Thanks to my lab mates
You have my eternal gratitude,
I'm no good at poems
So I think I should conclude.*

*I'm away to be a medic
I don't want them to think "he just legged it",
I wish you all the best
It's just a shame about this Brexit.*

Acknowledgments

I would like to thank my supervisors Dr. Joëlle Prunet and Prof. Rob Liskamp for giving me the chance to carry out my PhD in their research groups. Over the last 4 years they have always made time for me and I am indebted to them for their support and guidance. Being able to observe the way they each approach problems, scientific research and work in general has allowed me to develop from a student into a researcher.

My PhD has been made memorable by many members of the Raphael Lab and I would like to say thank you to Stéphane Wittmann, Aurélien Letort, Alexandre Audic, Amaia Altuna, Liam Adair, Alan Jeuken, Alex Ftiniakos and Carolina Ojeda. Also, thanks to the Liskamp Lab for being so hospitable when I wanted to borrow chemicals or ask for advice, in particular Helmus Van de Langemheen who often offered great support. Thanks to them all.

Having parents that live close by is a comfort that many PhD students have to do without, however I have been very fortunate that mine were by my side the whole time. Thank you both for everything (in particular inviting us for Sunday dinners).

Finally, thank you to my fiancée and partner in crime, Irene Cascallana Matías. We managed to successfully navigate our journey as PhD students! I'm going to miss walking home together each telling the other about our daily news. Not to worry, onto the next chapter together. Te quiero.

Abbreviations

AA: Allyl acetate
Ac: Acetyl
AIBN: Azobisisobutyronitrile
Ala: Alanine
ALG: Allyl glycine
ArC: Quaternary aromatic carbon
Arg: Arginine
Asp: Aspartic acid
ATRP: Atom transfer radical polymerisation
Bn: Benzyl
b.r.s.m: Based on recovered starting material
Cat: Catalytic
CM: Cross-metathesis
d: day
DIPEA: *N,N*-Diisopropylethylamine
DMAP: 4-Dimethylaminopyridine
DMF: Dimethylformamide
DMI: 1,3-dimethyl-2-imidazolidinone
DMPA: 2,2-Dimethoxy-2-phenylacetophenone
DMSO: Dimethyl sulfoxide
Et: Ethyl
Equiv: Equivalent
Gly: Glycine
h: hour
HMPA: Hexamethylphosphoramide
Leu: Leucine
MEK: Methyl ethyl ketone
Min: Minute
Mn: Molecular weight (number average)
mPEG: Methoxypropylene glycol
Mw : Molecular weight (weight average)
N: Molar
NMR: Nuclear magnetic resonance
PAGE: Poly(allyl glycidyl ether)
PEO: Poly(ethylene oxide)

Ph: Phenyl

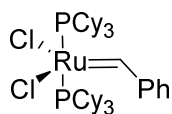
RCM: Ring-closing metathesis

SM: Self-Metathesis

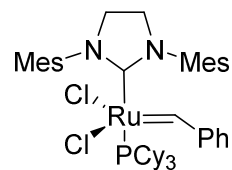
TBAB: Tetra-*n*-butylammonium bromide

THF: Tetrahydrofuran

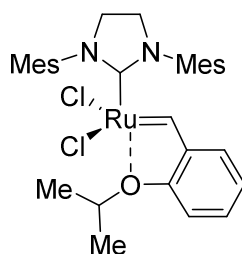
Table of RCM catalysts



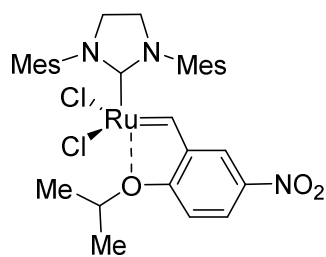
Grubbs 1
first generation
of Grubbs' catalyst



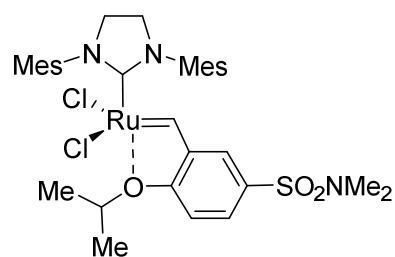
Grubbs 2
second generation
of Grubbs' catalyst



Hoveyda-Grubbs 2
second generation of
Hoveyda-Grubbs' catalyst



Grela
modified second generation
of Hoveyda-Grubbs' catalyst



Zhan-1B
modified second generation
of Hoveyda-Grubbs' catalyst

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Chapter 1 : Introduction

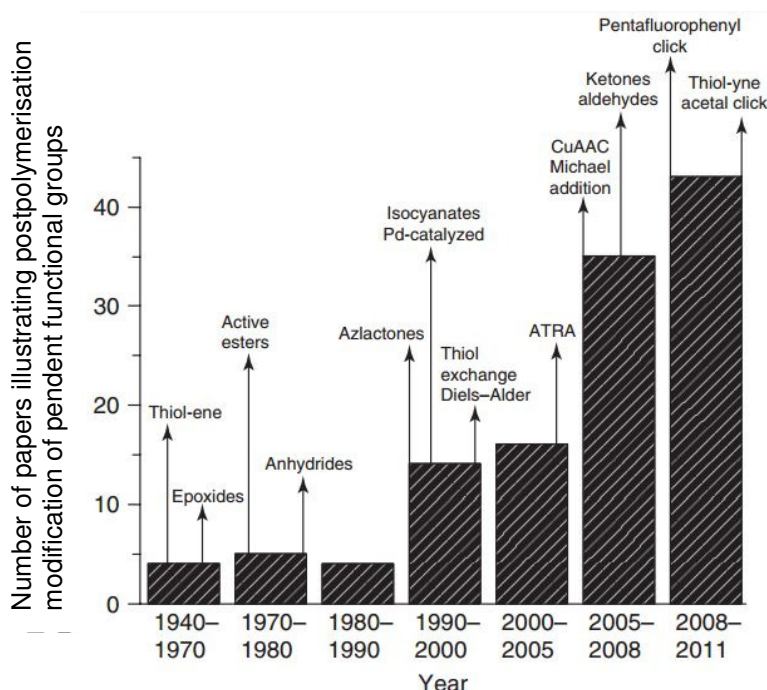
1.1 History

The area of polymer functionalisation dates back to 1840 with the discovery of vulcanised rubber.^[1] Reported independently by both Ludersdorf and Hancock this process of heating natural rubber, poly(*cis*-isoprene) with sulfur, produced a material that was more durable and less prone to cracking than its precursor. The ability to modify the chemical and physical properties of polymers, to create more pertinent materials, hailed a new era in materials science.

Polymer functionalisation expanded into a variety of industries. In 1865, Schützenberger reported the synthesis of cellulose acetate by heating cellulose with acetic anhydride.^[2] This new material was found to be a good replacement for nitrate film, a material commonly used by the film industry (for photographic film) and healthcare industry (as X-ray film). In 1922 Hermann Staudinger proposed the general structure of polymers that is accepted today.^[3] He suggested that macromolecules were the product of many small monomers covalently bonded together.^[4] This was initially met with much speculation especially by colloid chemists, since at the time macromolecules were defined as colloids/aggregates of multiple small molecules.^[3] Examining the chemistry of the monomers allowed for the synthesis of polymers with controlled properties such as strength, malleability, conductivity, degradability, and optics. This was revolutionary, since the start of the 20th century was focused primarily on replicating natural polymers; *i.e.* Chardonnet's report in 1883 on the synthesis of artificial silk by spinning concentrated nitrocellulose,^[5] and Hoffmann's report in 1907 on the synthesis of natural rubber by addition polymerisation. Staudinger was ultimately awarded the Nobel Prize for his work in 1953.

Staudinger polymer model led to an increase in post-polymerisation functionalisation techniques. In 1948, Serniuk *et al.* reported the conjugation of polybutadienes with aliphatic thiols via thiol–ene addition.^[6] In the 1950's the chlorination of polystyrene–divinylbenzene beads were developed as ion exchange resins.^[7] In 1963, Merrifield used a halogenated polymer to develop solid-state peptide synthesis by attaching amino acids to the electrophilic chlorinated sites.^[8] However, until this point the modifications of polymers were limited in that the functionalisation methods were not quantitative. This was in large part due to the difficulty at the time to produce polymers with a range of functional handles with controlled dispersity. However, this changed in the 1990's with the emergence of new functional group-tolerant polymerisation techniques such as atom-transfer radical

polymerisation (ATRP),^[9] reversible addition-fragmentation chain transfer (RAFT),^[10] nitroxide-mediated radical polymerisation (NMP),^[11] and single-electron transfer living radical polymerisation (SET-LRP).^[12]



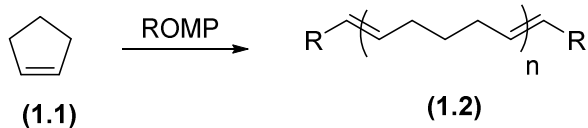
Graph 1 - Timeline of post-polymerisation modifications ^[13]

Due to the difficulty often associated with the purifications of polymers, it is desirable to develop reactions that require low catalytic loadings, and give low quantities of side products. It is for these reasons that click reactions have generated a great deal of interest in recent years.^[1]

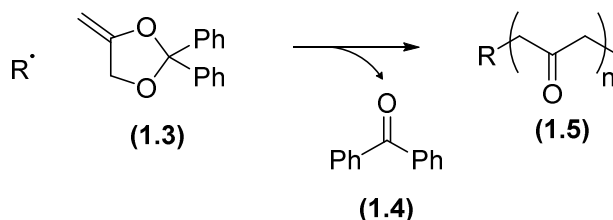
1.2 Overview of polymerisation process

The classification of polymers can sometimes be a confusing process, as polymers can fall into many different groups depending on the criteria being discussed. For example, the ring-opening metathesis polymerisation (ROMP) of cyclopentene **1.1** (Scheme 1.1) can be considered as a chain-growth polymerisation, but also as an addition reaction, whereas radical polymerisation of dioxolane **1.3** is also a chain-growth polymerisation, but releases benzophenone as a by-product, and is therefore a condensation polymerisation. Figure 1.1 shows a non-extensive summary of possible criteria pertaining to polymers. This project will focus on the anionic ring-opening polymerisation (ROP) of oxiranes in a chain-growth polymerisation (CGP).

Addition Chain-Growth Polymerisation



Condensation Chain-Growth Polymerisation



Scheme 1.1 – Examples of addition chain-growth polymerisation (CGP) and condensation CGP.

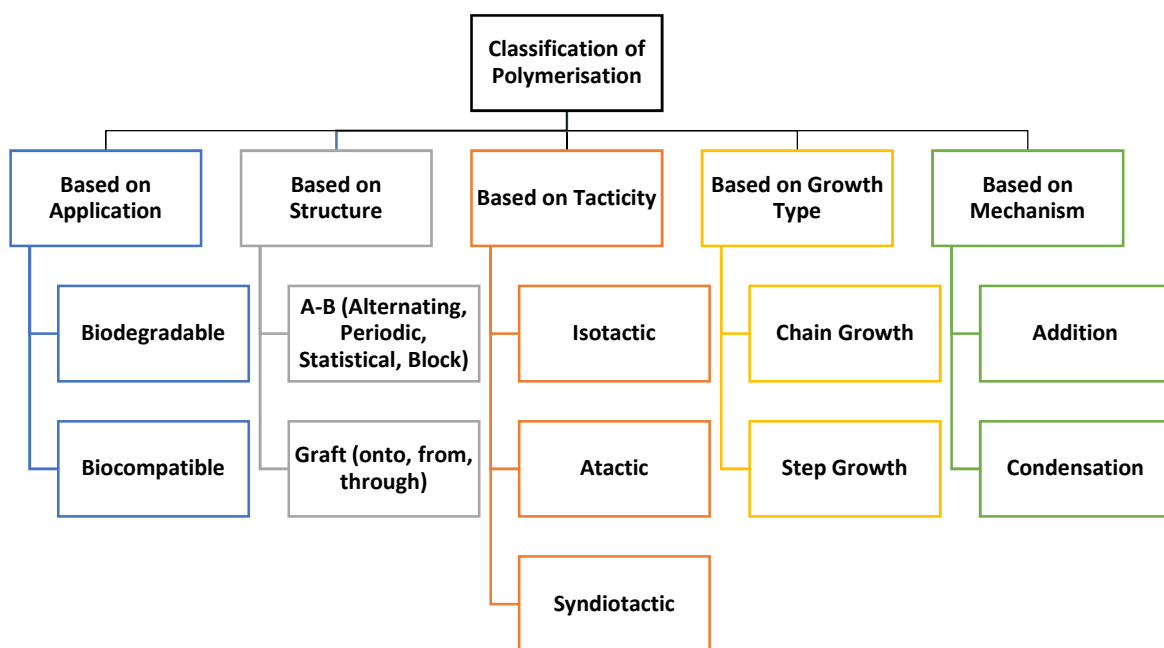


Figure 1.1 – Non-extensive summary of the classifications of polymerisation based on specific criteria.^[14]

1.2.1 Calculating polymer dispersity

The dispersity of a polymer is a measure of how even in length the polymer strands are. A dispersity of 1.00 would indicate a monodisperse material where all strands are equal in length. This is calculated by considering the number average molecular weight, M_n , and the weight average molecular weight, M_w .

M_n is simply the total weight of all the polymer strands divided by the number of polymer strands present. It does not convey any information about how varied the polymer lengths are, however it does indicate what the average molecular weight is (Equation 1).

$$M_n = \frac{\sum N_i \times M_i}{\sum N_i} \quad \text{Equation 1}$$

N_i = number of strands with mass M_i .

On the other hand, M_w factors into account how common a particular chain length is, relative to all other polymer chains in the sample. This is done by first calculating the *weight fraction*, W_i , which is the fraction of the total sample that a particular chain length represents (Equation 2).

$$W_i = \frac{N_i \times M_i}{\sum N_i \times M_i} \quad \text{Equation 2}$$

Summation of all the weight fragments ($\sum W_i M_i$) will then give the weight average molecular weight of the polymer (M_w), (Equation 3).

$$M_w = \sum W_i \times M_i = \frac{\sum N_i \times M_i^2}{\sum N_i \times M_i} \quad \text{Equation 3}$$

Comparison of M_n and M_w as a ratio is referred to the dispersity (\mathcal{D}). Overall, the ability to control the dispersity of a polymerisation is normally desirable, and so generally a value close to 1.00 is optimal, although this depends on the application of the polymer.

$$\mathcal{D} = \frac{M_w}{M_n} \quad \text{Equation 4}$$

1.3 Polyethylene Glycol (PEG) / Polyethylene Oxide (PEO)

The focus of this thesis is on the post-polymerisation functionalisation of various species of poly(ethylene glycol) (PEG) and poly(ethylene oxide) (PEO), synthesised by ROP of epoxide monomers. This section will focus on the applications of PEG derivatives as well as discuss the synthesis of PEG/PEO polymers. Note that the terms PEG and PEO are

often used interchangeably, however polymers with $M_n < 20,000 \text{ g.mol}^{-1}$ are referred to as PEG, whereas polymers with $M_n > 20,000 \text{ g.mol}^{-1}$ are referred to as PEO (Figure 1.2).^[15]

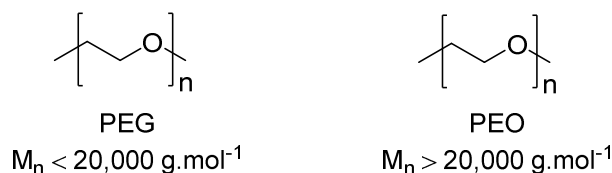


Figure 1.2 - PEG and PEO

1.3.1 Biomedical Applications of PEG/PEO

A variety of conjugated proteins are made naturally in the body via post-translational modifications such as phosphorylation, acylation, glycosylation, sulfation and methylation.^[16] These modifications can alter the chemical properties of the protein such as cell-signalling, targeting, metabolism, as well as modify the native proteins circulation time in the body.

It is estimated that up to 90% of current drugs and/or drug candidates suffer from poor aqueous solubility, which could in turn result in poor bioavailability.^[17,18] Bioactive compounds including peptides, proteins or other molecules are commonly coupled with PEG via a process called PEGylation. This can improve the pharmacokinetics of the bioactive compound, often by reducing the half-life of the drug-moiety.^[19] PEGylated drugs typically experience reduced renal filtration, decreased uptake by the macrophage system, and decreased degradation by enzymes.^[20,21]

Medium size drugs are typically conjugated to PEG with molecular weights ranging from 20 kDa to 50 kDa.^[21] This coupling to the high molecular weight PEG helps primarily to decrease the kidney filtration of the drug. These high molecular weight PEGs are also less prone to biodegradation than low molecular weight PEGs.^[15]

Larger drugs such as antibodies are more commonly bound to lower molecular weight PEG ranging from 1 kDa to 5 kDa.^[21] This helps to limit targeting by the macrophage system, decrease enzymatic degradation, and hide cationic charges. This reduction in kidney filtration of a PEGylated drug, due to large hydrodynamic volumes, can also be beneficial to drug delivery in anti-cancer therapeutics, as large nanoparticles have shown a propensity to accumulate in cancerous tissue. This is referred to as the enhanced permeability and retention (EPR) effect, and was first reported by Maeda *et al.*^[22] This ability of nanoparticles to apparently target tumours is generally explained by the need for the cancer cells to grow rapidly resulting in the stimulated production of blood vessels (hypervascularisation). The growth of these connected endothelial cells are unorganised and less tightly packed than

normal, allowing nanoscopic particles to enter and remain inside the neoplastic tissue. Lack of lymphatic drainage also prevents the clearance of these nanoparticles (Figure 1.3), overall resulting in accumulation in the tumour.^[23]

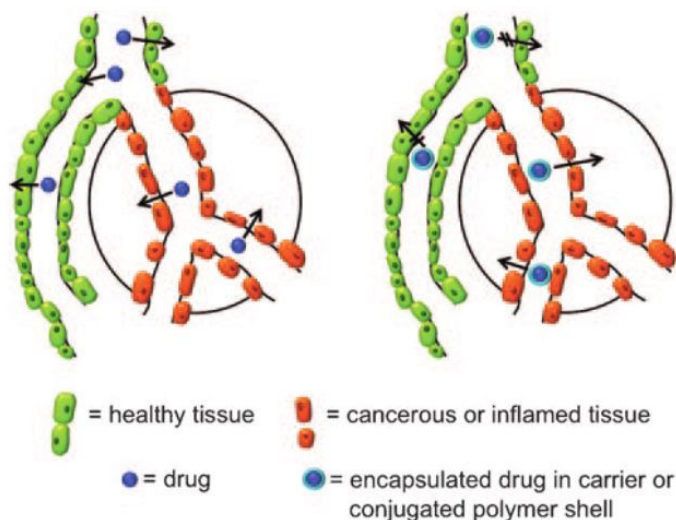


Figure 1.3 - Influence of the drug-polymer conjugate on drug delivery due to EPR effect.^[21]

In 2004, Kim *et al.* observed this EPR effect when studying polymeric micelles (PM) of methoxy-PEG (mPEG) loaded with paclitaxel (PTX).^[24] This polymeric prodrug (Genexol-PM[®]) offered increased delivery of PTX to the tumour cells,^[25] and Genexol-PM[®] has now been approved by the FDA for use for treating patients with breast cancer.^[26]

Overall, PEG itself is a very suitable candidate for many biological application due to its high solubility in a range of aqueous and organic media,^[27] low toxicity,^[19] resistance to biodegradation,^[15] and ease of excretion.^[28] Additionally, PEG can be synthesised in low dispersity, in line with the pharmaceutical standard of $\bar{D} = 1.10$.^[16,21] This desire for monodispersity is driven by the need for reproducible criteria such as body clearance times and cell targeting. Polymer-drug conjugates that are polydisperse can result in a broad half-life, which is an undesirable uncertainty when administering medication.

Limitations of PEG

The limitations of PEG can generally be divided into three groups i) adverse side effects that arise from either the polymer itself, or the side products that can be formed during the synthesis of the polymer, ii) changes in the pharmacokinetics of the drug-PEG conjugate, or iii) side effects from the low biodegradability of the PEG.^[21]

Adverse side effects

PEG has been shown undergo *non-specific* interaction in the body, such as potentially inducing blood clotting when delivered intravenously.^[21] However, PEG has also been shown to undergo *specific* recognition by the immune system. This can ultimately lead to hypersensitivity reactions (HSR) and anaphylactic shock.^[29] The exact origin of this response is not fully understood. One possibility is that the terminal hydroxyl groups of the PEG could provide molecular sites for the hydrolysis of C3 protein in the bloodstream.^[21] This fragmentation of C3 protein can lead to a biochemical cascade, leading to the polymeric surface being labelled as a foreign body by the immune system. However, many PEG products are based on methoxypolyethylene glycol (mPEG), which should prevent this immunological response. Overall, the exact cause of HSR is not fully understood, however the possibility of PEG to induce an immunological response should always be kept in mind.

Changes in the pharmacokinetics

PEG has also been shown to result in accelerated blood clearance (ABC). This is a phenomenon whereby a preceding injection of PEGylated-drug can influence the circulation time of subsequent PEGylated-drug injections. This was first observed by Dams *et al.* while studying the retention time of 2,000 kDa mPEG liposome in rats.^[30] Upon the first injection, the concentration of mPEG liposome after 4 hours was found to have reduced to $52 \pm 3.7\%$, however upon a second injection the concentration in the blood was significantly reduced after 4 hours to $0.6 \pm 0.1\%$.

It is believed that the mechanism for this process stems from the production of an anti-PEG antibody, IgM, which is produced upon the first injection.^[31] This leads to binding of the IgM to the PEG upon a second injection, resulting in hydrolysis of the C3 protein, leading to an immunological response. This results in uptake of PEG by the Kupffer cells, and rapid accumulation of the non-biodegradable PEG in the liver.

Low biodegradability

High molecular weight PEG has been shown to have low biodegradability, which can result in problems for excretion. Typically PEG is excreted in the urine and faeces, however high molecular weight PEG can accumulate in the liver and may lead to macromolecular crowding (also called macromolecular syndrome), a process that can drastically change the behaviour of cells.^[16] This occurs when high concentration of large molecules effectively reduce the volume of solvent, leading to abnormal cell behaviour.

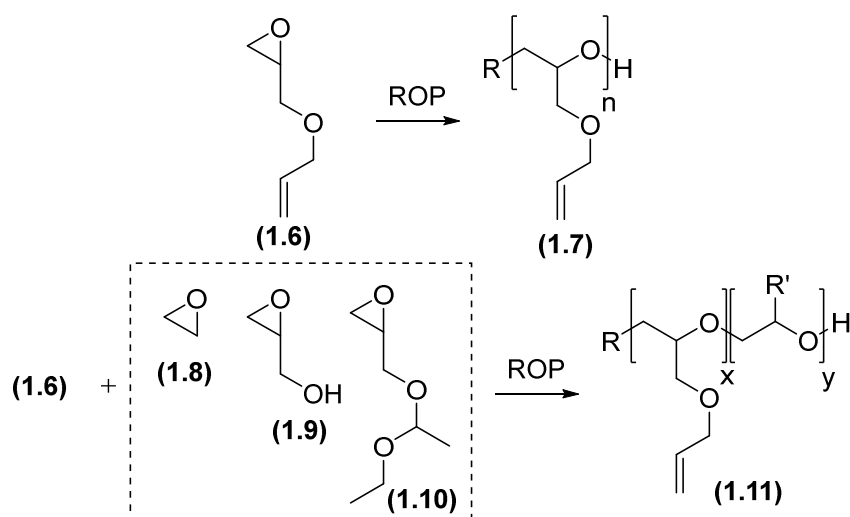
Typically the Bowman's capsule of the kidney has a protein clearance limit of ~60 kDa (albumin), however due to the hydrophilicity of PEG, the hydrodynamic volume of the polymer is typically 2-5 times greater than the a globular protein of the same molecular

weight.^[16] Overall, the upper limit for urinary excretion of PEG is ~30 kDa, above which excretion in the faeces is the more predominant excretion route.

PEG remains one of the most widely used polymers in biomedical applications due to its ability to increase the bioavailability of drugs whilst allowing for limited toxicity.^[21] Additionally, utilisation of the EPR effect can prove a valuable tool for targeting cancerous cells. Unfortunately the possibility of hypersensitivity, accelerated blood clearance and low biodegradability, has been shown to be problematic in some PEG applications.

1.3.2 Polyallyl glycidyl ether (PAGE)

Although PEG has found many uses, the lack of functional handles along the polymer backbone limits the possible modification of the material. Use of an allylic functional group allows for a range of post-polymerisation modifications to be carried out, whilst being innocuous to anionic ROP polymerisation. Poly(allyl glycidyl ether), PAGE **1.7** has been previously synthesised as a homopolymer as well as a copolymer **1.11** with various oxirane monomers including ethylene oxide (EO) **1.8**, glycidol (G) **1.9** and ethoxy ethyl glycidyl ether (EEGE) **1.10** (Scheme 1.2).^[32–38] Post-polymerisation modification of AGE polymers has also been performed by utilising thiol-ene chemistry.^[36,39,40]

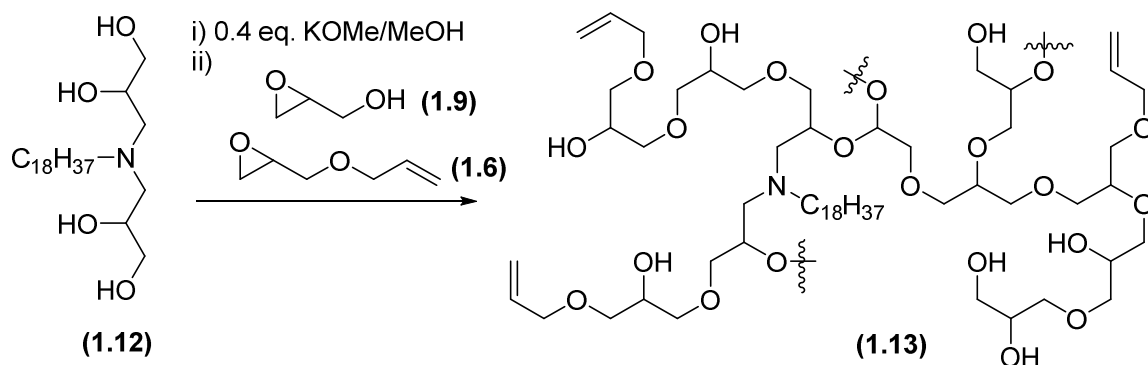


Scheme 1.2 – Various polymers of allyl glycidyl ether.

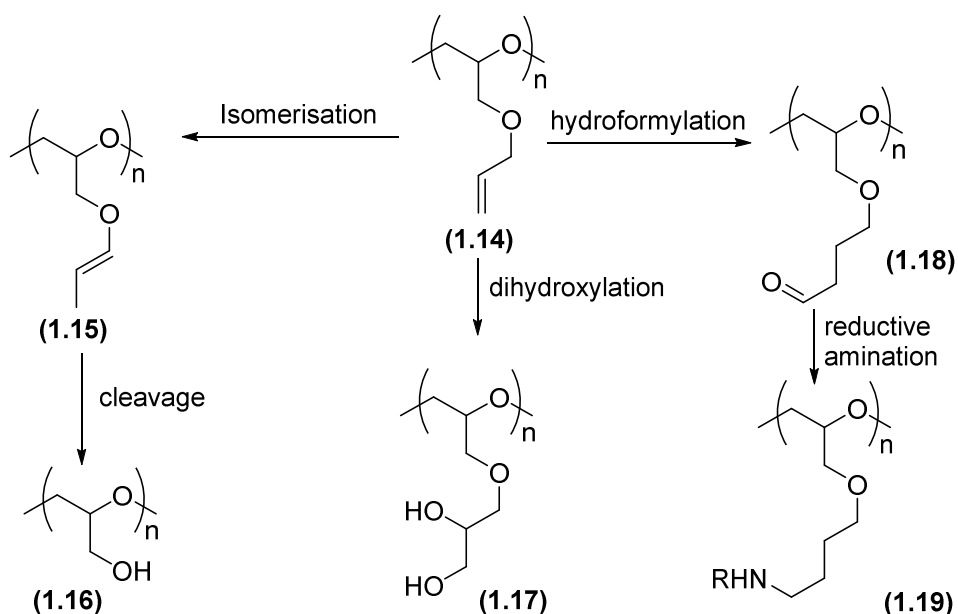
PAGE Synthesis

In 2000, Sunder *et al.* achieved the synthesis of hyper-branched polyethers, PG-*co*-PAGE **1.13** by the copolymerisation of glycidol **1.9** and allyl glycidyl ether **1.6**.^[32] This was done by using bis(2,3-dihydroxypropyl)octadecylamine **1.12** in a base catalysed random copolymerisation to synthesise the hyper-branched copolymers **1.13** in controlled degree of polymerisation (DP), with a dispersity of $\mathcal{D} \sim 1.7$, and controlled degree of branching (DB)

(Scheme 1.3). A small fraction (<5%) of the alkenes underwent isomerisation to the *trans*-1-propenyl isomer **1.15** during the polymerisation process (Scheme 1.4). Interestingly, they showed that this pendent allyl group could undergo a number of post-polymerisation transformations; (i) cleavage of the allyl groups, resulting in 1,3-glycerol units **1.16** bearing primary hydroxy groups; (ii) dihydroxylation of the double bond, leading to polyglycerols **1.17** with greatly increased polarity, and (iii) hydroformylation to aldehyde **1.18** followed by reductive amination and protection to amine **1.19**, highlighting the ability to achieve orthogonality between the hydroxyl and allyl groups.



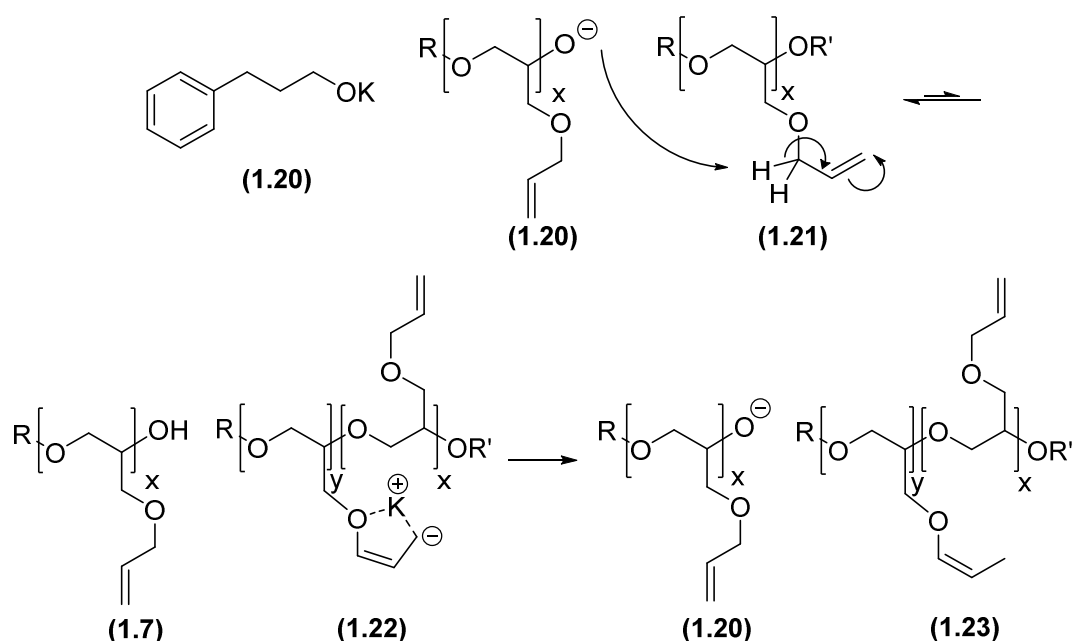
Scheme 1.3 – Polymerisation of glycidol and allyl glycidyl ether to yield hyperbranched copolymers.^[32]



Scheme 1.4 – Post-polymerisation modifications of PG-co-PAGE by Sunder *et al.*^[32]

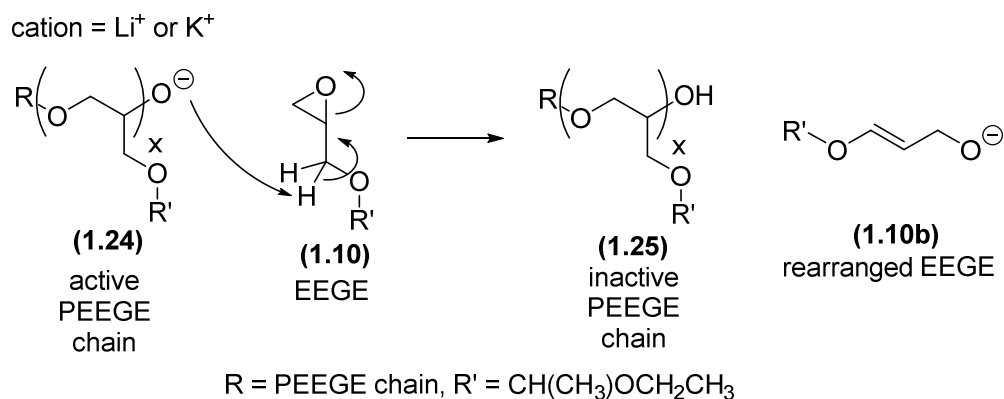
In 2007, Erberich *et al.* studied the synthesis of PAGE **1.7** as a protecting group for the production of polyglycidols.^[33] Use of potassium alkoxide **1.20** as an initiator allowed for the

production of PAGE **1.7** with good dispersity ($\bar{D} = 1.27$), however only 80% conversion could be achieved. The group propose that as the reaction proceeds the decreasing monomer concentration allows a side reaction to occur, whereby the propagating alkoxide chain **1.20** abstracts proton from the allylic position of either a monomer or a polymer's pendent allyl group **1.21**. This protonation of alkoxide **1.20** results in chain termination. However this process presumably results in the isomerisation of alkene **1.21** to 1-propenyl species **1.23** (Scheme 1.5),^[37] although the group do not mention this. Additionally, the group noted the gelation of the PAGE **1.7** after having been left to stand for several days, which they propose might have occurred by a radical or ionic process, although this is not investigated further.



Scheme 1.5 – Chain termination/Isomerisation of AGE

Hans *et al.* have studied the chain transfer (as opposed to chain termination) of EEE **1.10** via ROP using both lithium and potassium based alkoxide initiators.^[35] Polymerisation proceeded with full conversion and good dispersity ($\bar{D} = 1.09 - 1.19$), although the observed M_n was consistently 10% higher than the calculated M_n . Additionally, the dispersity increased with increasing ratios of [monomer]:[initiator]. The group observed that one of the methylene protons of **1.10** underwent abstraction by propagating alkoxide chain **1.24**, resulting in chain transfer (Scheme 1.6) and production of allyl alkoxide **1.10b**. This alkoxide was then able to reinitiate the polymerisation, however this process did limit the M_n to 30,000 $g.mol^{-1}$. The reaction conditions were varied to prevent this proton abstraction process and overall found that it could be reduced by use of potassium based initiators as opposed to lithium. This is explained by the potassium species exhibiting decreased basicity and increased nucleophilicity, thus resulting in decreased chain transfer compared to lithium.



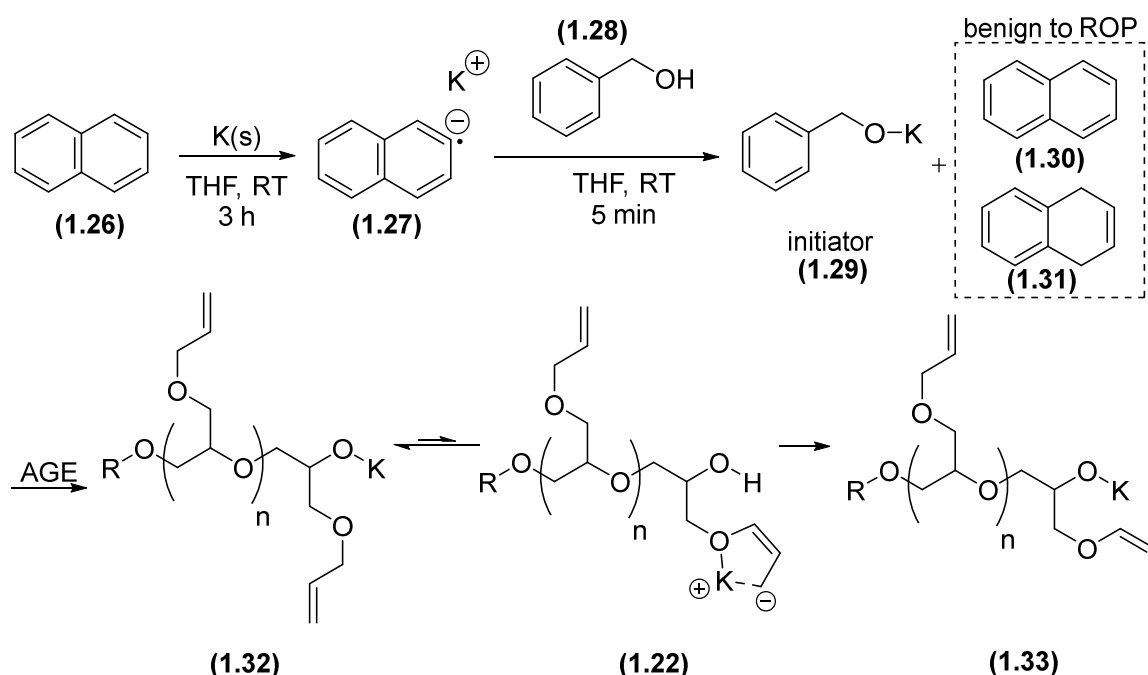
Scheme 1.6 – Chain transfer from propagating PEEGE chain to monomer

In 2010, Obermeier and Frey utilised a caesium alkoxide initiator to produce PEO-*co*-PAGE in very good dispersity ($\mathcal{D} = 1.02 - 1.05$).^[36] Caesium initiators exhibit more ionic character than potassium based initiators, which increases the reactivity of the propagating chain. Additionally, Cs^+ ions are less efficient at alkene isomerisation. However, the caesium based initiators such as caesium 2-methoxyethoxide were poorly soluble in THF, and so addition of DMSO was required. Polymerisation in benzene used PEG ($M_n > 1000 \text{ g mol}^{-1}$) as a macro-initiator by deprotonating both termini of the PEG with CsOH . Unfortunately, polymerisations could only be carried out up to $10,000 \text{ g mol}^{-1}$.^[36] This is most likely the result of *chain termination*, caused by protic impurities such as water that was produced during the initiator synthesis.^[37] The authors also reported the isomerisation of the terminal olefin to the *trans*-enol ether. This occurred readily when the polymerisation was carried out at both 100°C and 60°C , although lowering the temperature to 40°C reduced the degree of isomerisation to $<10\%$.

Up until this point, many of the initiators of AGE **1.6** relied on the use of strong, non-nucleophilic bases after the removal of the conjugated acid e.g. *tert*-butanol, in order to generate an alkoxide that could function as an initiator when AGE was added.^[37] In 2011, the Hawker group. proposed that these strategies allowed for the introduction of protic impurities e.g. alcohols or water, which can lead to problems during polymerisation such as chain termination.^[37] Instead, they investigated the use of the radical-anion potassium naphthalenide **1.27**, titrated with benzyl alcohol **1.28** to yield potassium alkoxide initiator **1.29**, which was then used to polymerise AGE (Scheme 1.7). Notably this method produced naphthalene **1.30** and dihydronaphthalene **1.31** by-products, which are inert to the anionic ROP polymerisation. This method allowed for PAGE to be synthesised with controlled DP, excellent dispersity (\mathcal{D} between 1.05 and 1.20) and quantitative conversion; however it was observed that higher M_n PAGE ($M_n > 90 \text{ kg mol}^{-1}$) experienced an increased dispersity ($\mathcal{D} \sim 1.33$). It was proposed that these increases in dispersity occurs due to either radical coupling of the pendent allyl groups, or chain coupling occurring after the polymerisation

has achieved full conversion. Unfortunately, no details are discussed regarding the mechanistic feasibility of these processes. This is different from the chain termination reactions as observed by Erberich *et al.*^[33] as well as being different from chain transfer as had been observed by Hans *et al.*^[35]

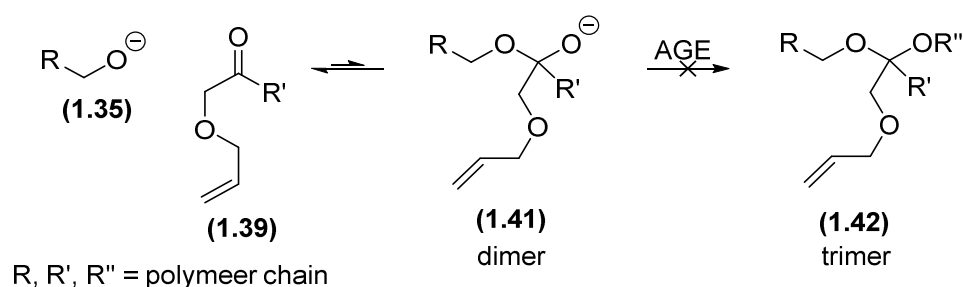
Hawker *et al.* also reported the occurrence of isomerisation of the allylic group of **1.32** to the *cis*-enol ether **1.33**,^[37] which was in contrast to the *trans*-isomer **1.15** reported by Sunder *et al.*,^[32] as well as Obermeier and Frey (Scheme 1.7).^[36] The group proposes that deprotonation by the alkoxide chain **1.32** at the allylic position leads to the alkyl potassium species **1.22** in a 5 membered cyclic intermediate. Subsequent deprotonation of a dormant hydroxylated chain by carbanion **1.22** could then reinitiate the polymer propagation, whilst leaving olefin **1.33** in a *cis* configuration. Although Erberich *et al.* believed this allylic deprotonation resulted in chain termination (Scheme 1.5), Hawker *et al.* propose that it does not constitute chain termination since the reactive nature of the alkyl potassium intermediate **1.22** means that the isomerisation of the alkene is fast relative to the chain propagation. The Hawker group then go on to show that *cis*-propyl **1.33** could then be cleaved in methanol over a polymer-supported sulfonic acid resin (DOWEX) to produce a linear random copolymer with pendent allyl and hydroxyl groups.



Scheme 1.7 – Polymerisation of AGE by potassium alkoxide with possible isomerisation mechanism

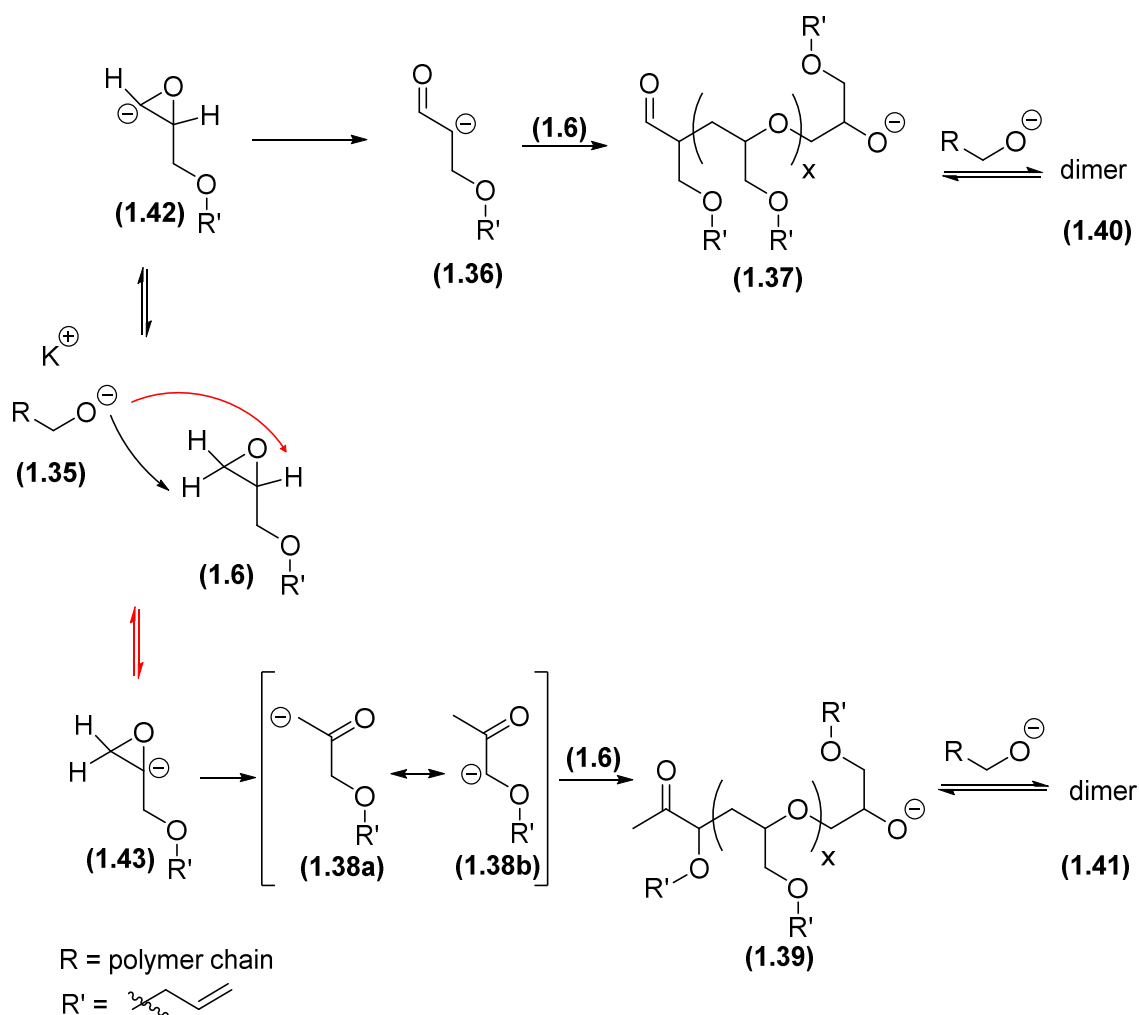
Finally, in 2015, Groll and Kuhlmann showed that the slow addition of the AGE monomer **1.6** to a potassium *tert*-butoxide initiator could be used to synthesise PAGE **1.7** in controlled dispersity.^[38] While synthesising PEEGE **1.25**, Hans *et al.* had observed the bimodal

distribution on the size exclusion chromatography (SEC) elugrams, with one peak being exactly twice the molar mass of the other, indicating the coupling of the polymer chains. Additionally Hans *et al.* had reported that an increase in the ratio of [monomer]:[initiator] led to an increase in this bimodal distribution, which Groll and Kuhlmann subsequently saw during the synthesis of PAGE **1.7**. Both groups suggest that this dimerisation, during the synthesis of PEEGE **1.25** and PAGE **1.7**, was likely due to the formation a ketone intermediate such as **1.39** that can undergo nucleophilic attack by a propagating chain **1.35** (Scheme 1.8).^[35,38,41]



Scheme 1.8 – Dimerisation of PAGE, rapid reversal preventing trimer formation.^[38]

Formation of this ketone enolate **1.38b** is probably formed by the deprotonation of monomer **1.6** by a propagating chain **1.35** allowing epoxide **1.43** to irreversibly open to form disubstituted enolate **1.38b**. This unstable intermediate will then tautomerise to the more stable trisubstituted enolate **1.38b**, which can then reinitiate the polymerisation reaction to yield the ketone capped propagating chain **1.39** (Scheme 1.9). Due to the lack of low molecular weight polymer on the SEC elugram, this ketone-alkoxide coupling to form dimer **1.41** must be reversible, and must only be pushed to completion when the concentration of monomer **1.6** decreases to zero *i.e.* when the reaction has achieved full conversion.^[38] Neither group mention the possible formation of the kinetically favoured aldehyde enolate monomer **1.36**, which, considering its high reactivity, should allow for rapid nucleophilic attack on epoxide monomer **1.6**. However recovery of solely hemiacetal **1.41** indicates that the rate of formation of aldehyde **1.37** must be slower than the equilibrium to form the thermodynamically favoured ketone enolate **1.38**.



Scheme 1.9 – Polymerisation of AGE by potassium alkoxide with possible isomerisation mechanism.

Groll and Kuhlmann propose that the equilibrium between the ketone capped chain **1.39** and dimer **1.41** is rapid in comparison to the propagation of the terminal alkoxide with AGE, therefore any dimer that is formed quickly breaks apart before it can form a trimer (Scheme 1.8). Therefore, slow addition of the AGE **1.6** should limit the monomer deprotonation side reaction that allows for formation of ketone enolate **1.38** in the first place, thereby limiting the ketone induced coupling responsible for the bimodal distribution.

In general, the group found that dispersity of PEEGE **1.25** was lower than PAGE **1.7** with the latter being more sensitive to the rate of monomer addition. When DP = 50, the dispersities of PAGE **1.7** could be reduced from 1.30 to 1.16 by slow addition (Figure 1.4), whereas dispersities for PEEGE **1.25** were reduced from 1.16 to 1.11. Additionally, these polymerisations were performed at 45 °C since the isomerisation reactions of the pendent allyl handles reported by previous groups,^[32,35–37] were suppressed at this temperature.

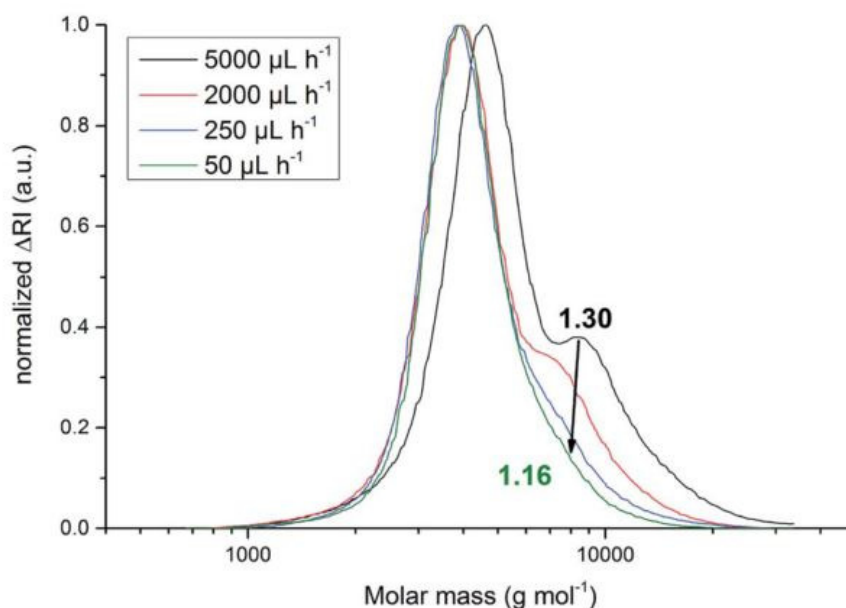


Figure 1.4 - Molar-mass distribution of PAGE. Decreasing the monomer feed rate from 5000 to 50 $\mu\text{L}\cdot\text{h}^{-1}$ reduces the dispersity from 1.30 to 1.16.

Overall, a range of techniques have been investigated to produce PAGE **1.7** in low dispersity, controlled DP, and high molecular weight, however side reaction of chain termination, chain transfer or isomerisation are often observed. These findings are summarised in Table 1.1.

	Polymer	Initiator	Chain termination	Chain transfer	Isomerisation	Dispersity
Sunder	PG-co-PAGE	K^+	None reported	None reported	trans	1.7
Erberich	PAGE	K^+	Deprotonation at allylic position	None reported	None reported*	1.27
Hans	PEEGE	K^+ and Li^+	None reported	Deprotonation of CH_2 adjacent to oxirane	N/A	1.09 – 1.19
Obermeier and Frey	PEO-co-PAGE	Cs^+	None reported	limited	trans	1.02 – 1.05
Hawker	pEO-co-PAGE	K^+	None observed by SEC	None observed by SEC	cis	1.05 – 1.33
Groll and Kuhlmann	PAGE	K^+	None reported	Ketone induced coupling	None reported**	1.16 – 1.30

* Although no isomerisation was reported, deprotonation at the allylic position should lead to isomerisation to the enol ether.

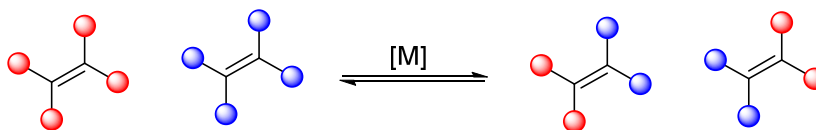
** Isomerisation suppressed by low reaction temperature (45 $^{\circ}\text{C}$).

Table 1.1 - Summary of PAGE synthesis by various groups.

Overall, PAGE has been investigated for a range of uses such as pH sensitive drug delivery, however many of these modifications are limited to thiol-ene click chemistry. Olefin metathesis could prove to be a useful method to install further functionality.

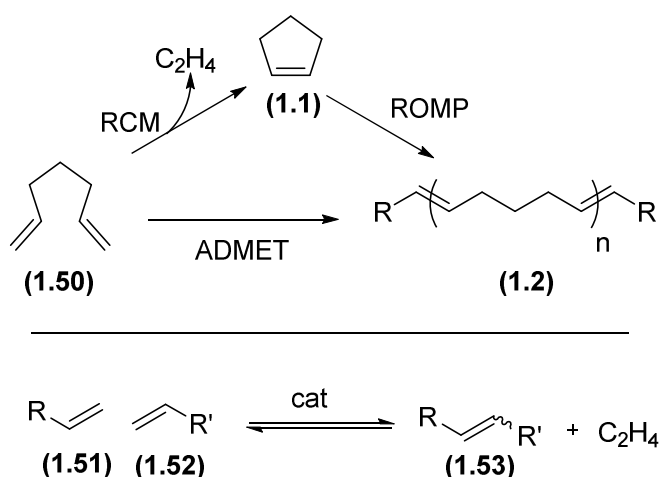
1.4 Olefin Cross Metathesis

Developed over 40 years ago, olefin metathesis is used to exchange the substituents of a double bonds between two alkene species. This results in the formation of new carbon-carbon bonds, with the aid of a transition metal catalysts. It was in 2005 that Yves Chauvin, Robert Grubbs and Richard Schrock received the Nobel Prize for their work in this field.



Scheme 1.10 – Simplified example of cross metathesis.

This exchange, represented in Scheme 1.10, can occur either intramolecularly or intermolecularly. If this occurs intramolecularly it is referred to as ring closing metathesis (RCM), as the reaction results in the formation of a cyclic structure such as **1.1**. This has the entropic driving force of producing two molecules from one, where one of these molecules is often gaseous ethylene (Scheme 1.11). Intermolecular olefin metathesis is referred to as cross metathesis (CM). If the CM reaction is occurring between two terminal alkenes **1.51** & **1.52** then the reaction will be pushed to completion by the evolution of ethylene, however in the cases of non-terminal alkenes, this driving force is lost. As a result CM is often more challenging than RCM.

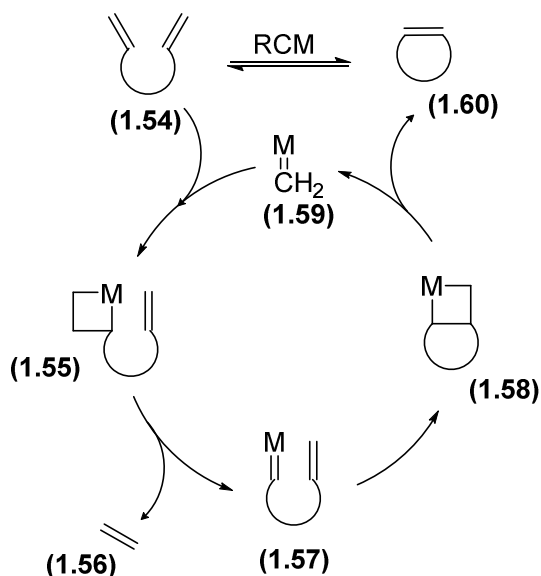


Scheme 1.11 - General scheme of olefin cross metathesis including CM, RCM, ROMP and ADMET.

Olefin metathesis has been used to develop new polymerisation reactions, namely ring-opening metathesis polymerisation (ROMP), acyclic diene metathesis polymerisation (ADMET), and ring-opening cross-metathesis (ROCM). ROMP, derived from RCM, occurs whereby a strained cyclic unsaturated monomer **1.1** undergoes metathesis with another monomer to yield a polymer chain. The driving force for ROMP is the release of the ring strain of the alkene monomer. This is a chain-growth polymerisation process due to the addition of a single monomer at a time. ADMET, derived from CM, occurs whereby a diene monomer **1.50** undergoes CM with another monomer in a step-growth polymerisation process.

Olefin metathesis was first observed by Ziegler whilst studying the use of organometallic complexes as catalysts in the synthesis of polyolefins.^[42] It was observed that, as well as catalysing the polymerisation of ethylene, some alkyl aluminium catalysts also produced but-1-ene as a side product. Further studies by the Philips Petroleum Co. showed that propene, with cobalt molybdate, yielded ethylene and but-2-ene, indicating a cross metathesis reaction of the olefin.^[43]

The accepted mechanism for this process was first proposed by Yves Chauvin in the 1970's (Scheme 1.12) by studying RCM of 1,7-octadiene as a substrate.^[44] The first stage is a [2+2] cycloaddition of a diene **1.54** with metal-methylene complex **1.59**, to yield cyclobutane intermediate **1.55**. Although a [2+2] cycloaddition is normally symmetry forbidden under thermal conditions, this process is able to proceed at room temperature as interaction between the *p*-orbitals of the alkene and *d*-orbitals of the metal lower the activation energy sufficiently by breaking the symmetry of the system.^[45] After this, the four-membered ring **1.55** undergoes cycloreversion to form a new carbene complex **1.57**, as well as affording the release of ethylene - an entropically favoured process which acts as a strong driving force. This is followed by a consecutive [2+2] cycloaddition between carbene of **1.57** with a second alkene. This four-membered **1.58** ring again collapses to yield the final cross-metathesis product **1.60**, and the regenerated metal carbene catalyst **1.59**.



Scheme 1.12 - Ring-Closing Metathesis catalytic cycle

In 1990, Richard Schrock published the synthesis of a molybdenum complex **Mo1** that was capable of efficiently carrying out this reaction (**Figure 1.5**).^[46] This reactive species offered a high turnover frequency (TOF) and would readily facilitate olefin metathesis. It was however limited in its tolerance of functional groups, especially protonated heteroatoms, as the electron deficient molybdenum will complex with the heteroatom, therefore disabling it as a catalyst.^[47] As a result, use of this catalyst must also be carried out in an inert atmosphere.

In 1992, Robert Grubbs developed a ruthenium type complex, **G1**, which was less moisture sensitive (**Figure 1.5**). Although less reactive than Schrock's molybdenum complex, this catalyst offers a greater degree of selectivity in the reaction, as well as being able to tolerate a broader range of functional groups. The Ru(II) of **G1** is a 16-electron d^6 coordinated centre complexed with two chlorine atoms, two electron-rich tricyclohexyl phosphine ligands, and a benzylidene ligand.

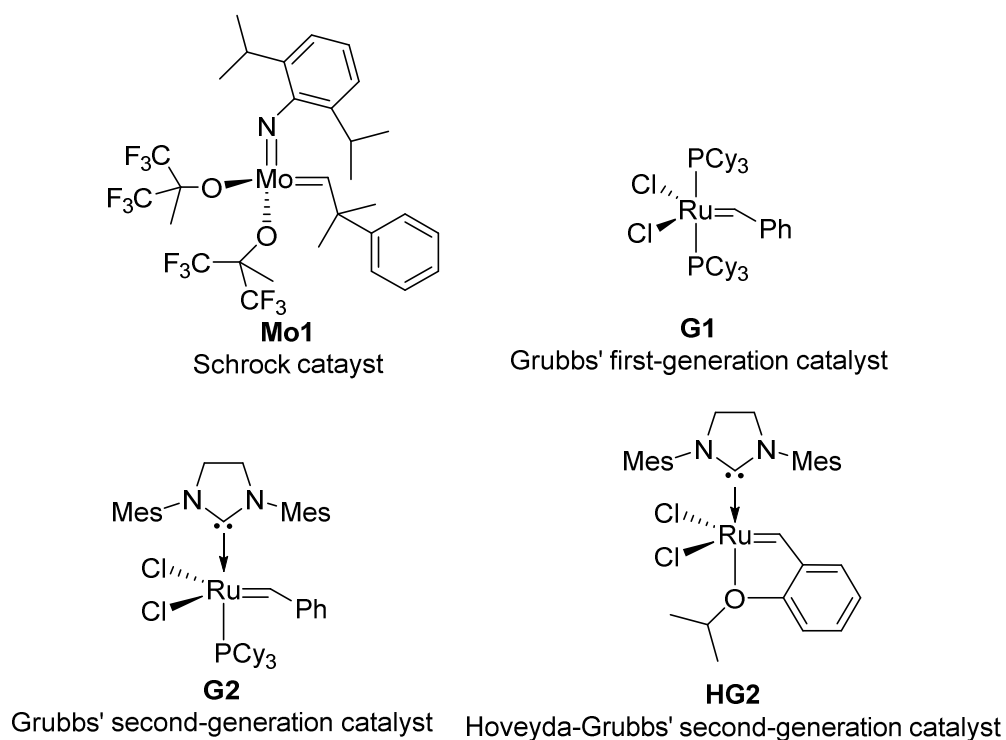
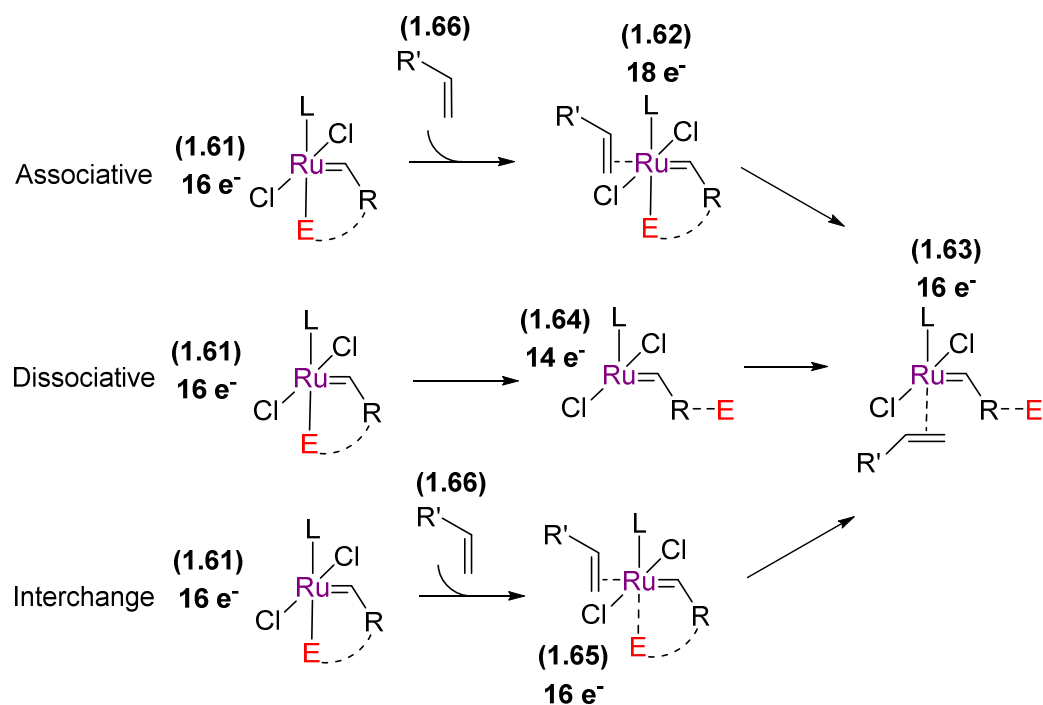


Figure 1.5 - Metathesis catalysts

The first stage in the catalytic cycle is the activation of the pre-catalyst, which can occur by three possible mechanisms; associative, dissociative and interchange (Scheme 1.13). With respect to **G1**, the activation of the catalyst from a 16 electron species **1.61** to a 14 electron species **1.64** occurs by dissociation of a PCy₃ group. This more reactive intermediate can then coordinate to a coupling partner **1.66** and continue with the catalytic cycle previously discussed.

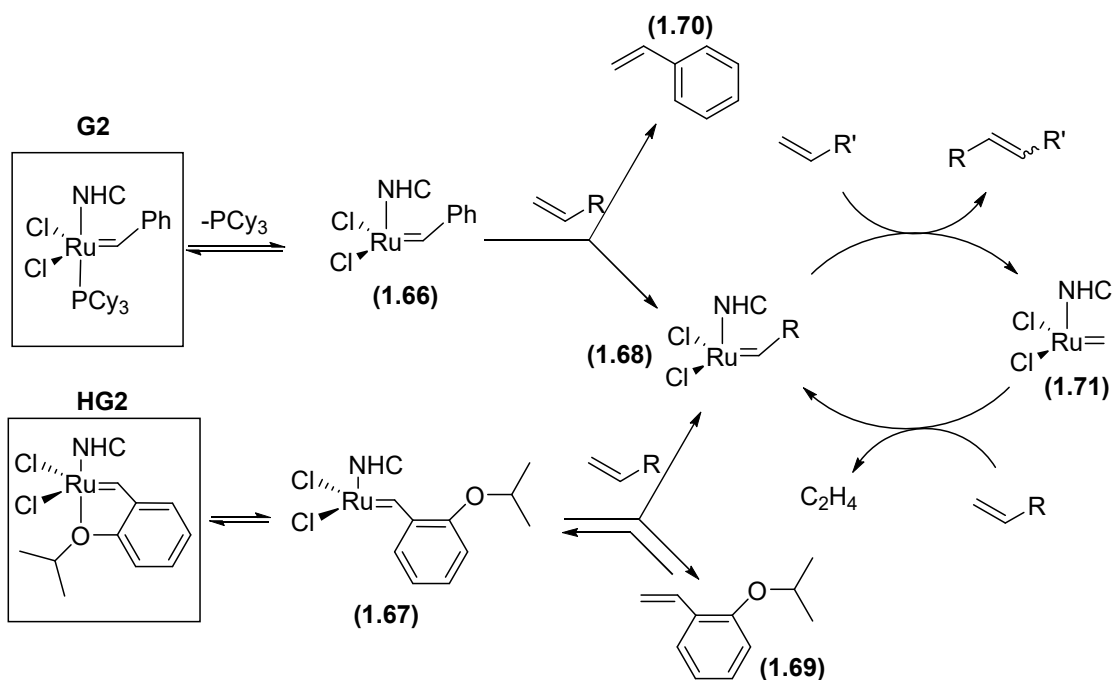
In the case of **G2**, the ruthenium is also in the Ru(II) oxidation state, however one of the phosphine ligands has been replaced by a *N*-Heterocyclic carbene (NHC) ligand. This NHC ligand acts as a strong σ -donator and weak π -acceptor, allowing it to stabilise the 14-electron intermediate **1.64**, which means that the catalyst is less reactive towards air and moisture. Activation of the **G2** catalyst occurs by a combination of the dissociative and interchange mechanism.^[48] In general, **G2** is a more active catalyst than **G1** because the rate of PCy₃ rebinding is slower in the case of **G2**, allowing for the catalyst to exist in the more CM active 14 electron species **1.64**.

In 2000, Hoveyda *et al.*^[49] and Blechert *et al.*^[50] reported almost simultaneously the development isopropoxystyrene-coordinated catalyst referred to as Hoveyda-Grubbs' second generation catalyst, **HG2**. Compared to the phosphine containing **G2**, the **HG2** catalyst shows increased thermal stability, and tolerance to both oxygen and moisture.^[45] In addition, **HG2** showed increased reactivity towards electron poor alkenes acrylonitriles, fluorinated alkenes, vinyl phosphine oxides, and sulfones.^[51]



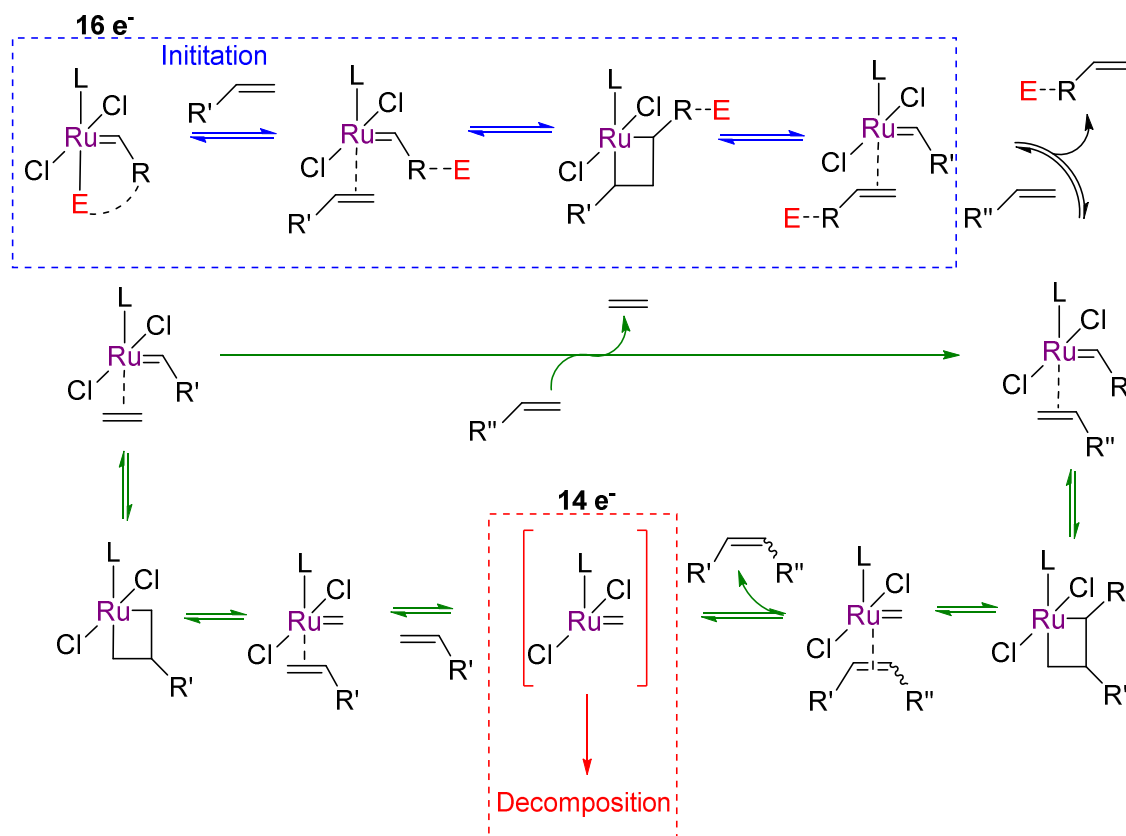
Scheme 1.13 – The possible mechanisms of pre-catalyst activation.^[48]

It is commonly believed that **G2** and **HG2** yield identical active catalyst **1.71** after the first catalytic cycle, however the well documented differences in reactivity (especially towards electron deficient alkenes) indicate that the mode of propagation must be different (Scheme 1.14).^[51] This difference is believed to be due to the “boomerang-effect” of the isopropoxystyrene, whereby **HG2** is in equilibrium with the 14 electron species **1.71**. This boomerang effect is not observed with the styrene of **G2**.

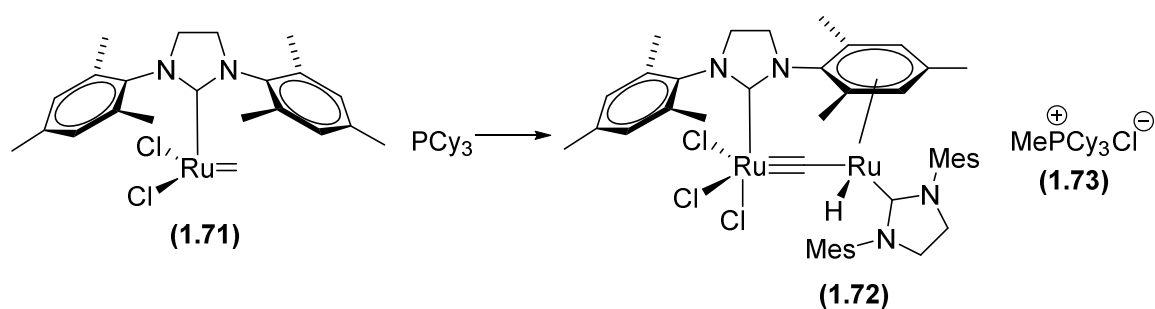


Scheme 1.14 – Comparison of **G2** and **HG2** catalytic cycles^[51]

During the CM catalytic cycle, the ruthenium centre goes through sequential cycloadditions and cycloreversions to yield various alkylidene complexes, and methylidene complex **1.71** (**Scheme 1.15**). This methylidene species is fragile and prone to degradation. In the case of **G2** this can occur by the phosphine abstracting the methylidene of **1.71** to produce a phosphonium salt **1.73**, leaving the ruthenium in a 12 electron state.^[52] This highly unstable complex can co-ordinate to a neighbouring methylidene complex **1.71** to form a bimetallic hydride **1.72** (**Scheme 1.16**).



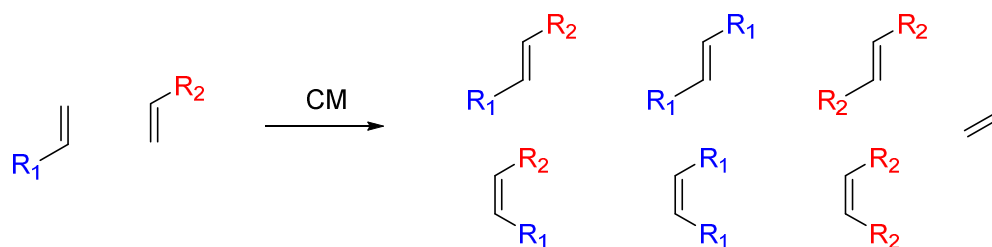
Scheme 1.15 – Catalytic cycle of the ruthenium catalyst.^[48]



Scheme 1.16 – Decomposition of methyldiene complex.^[48]

Alkene Selectivity

For the cross metathesis between two terminal alkenes, the products are dependent upon the chemical nature of the two alkenes. For example, the products of the intended metathesis could be either the *E* or *Z* isomer; however homodimerisation of each individual coupling partner could also occur, leading to a range of possible products (Scheme 1.17).



Scheme 1.17 - Potential products of olefin metathesis

The degree to which the desired cross metathesis takes place can be controlled by varying the equivalents of the starting material, but more importantly it is dictated by the chemical properties of each coupling partner. In general, olefins can be categorised into one of four types (**Table 1.2**).^[53]

Type of olefin	Product	Example
1	Rapid homodimerisation, and homodimers are consumable	Terminal olefins, allyl halides, allyl phosphonates, allyl silanes, allyl sulphides, styrenes with no large ortho substituent.
2	Slow homodimerisation, and the homodimers are slightly consumable	Acrylates, vinyl ketones, secondary allylic alcohols, styrenes with large ortho substituent.
3	No homodimerisation	1,1-disubstituted olefins, non-bulky trisubstituted olefins, vinyl phosphates, phenyl vinyl sulfone, tertiary allylic alcohols (protected)
4	Olefins do not partake in CM, however they do not hinder it by catalyst deactivation	Vinyl nitro olefins, trisubstituted allyl alcohols (protected).

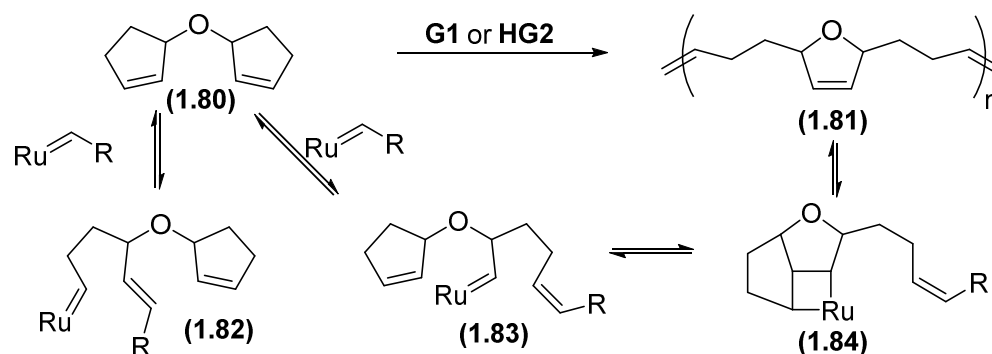
Table 1.2 - Types of olefin for Grubbs' second-generation catalyst.

Type 1 olefins all possess reactive electron-rich double bonds, and are prone to rapid homodimerisation, and so reacting a type 1 olefin with another type 1 olefin will yield a statistical mixture of products that is only influenced by the equivalents of starting materials used. The homodimer that is formed is however capable of subsequent metathesis reactions, so reacting a type 1 olefin with a type 2 or 3 alkene will eventually lead to the coupling of the two different partners (the thermodynamic product). Type 2 olefins are electron deficient or hindered and are less reactive to olefin metathesis than type 1 alkenes, and will slowly dimerise. The resulting dimers are typically type 4 in character, which do not normally participate in subsequent metathesis. Type 3 molecules do not homodimerise and so will only react with type 1 and type 2 olefins. Type 4 olefins do not undergo olefin metathesis, although they do not deactivate the catalyst. Coupling partners may fall into

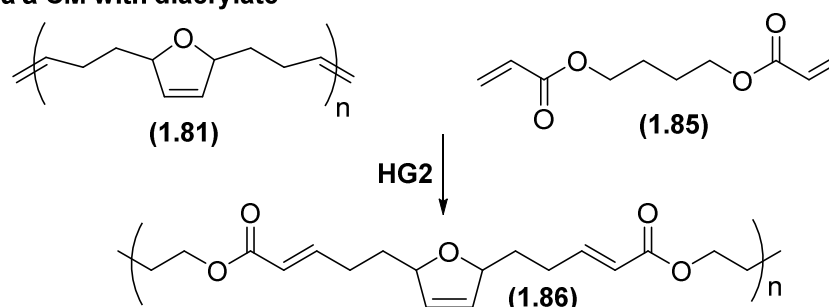
different classifications depending on the catalyst used, although in all cases the deciding factors come down to steric bulk and electron deficiency of the olefin.

The *cis/trans* stereochemistry of the alkene product is reliant on the reaction being reversible. This means that the reaction will reach its thermodynamic product, which is almost always the *E*-alkene. The exception to this is the case of small-ring forming RCM, which will be unable to give an *E*-alkene due to ring strain.

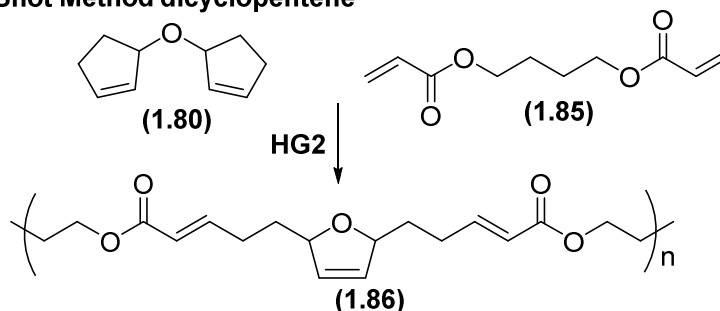
RO/RCM of dicyclopentene



MOMP via a CM with diacrylate



MOMP via a One-Shot Method dicyclopentene



Scheme 1.18 – RO/RCM/CM of dicyclopentene.

An example that nicely showcases many of these olefin metathesis reactions in action was reported by Grubbs *et al.* whilst development of a new type of polymerisation; tandem ring-opening metathesis/ring-closing metathesis (ROM/RCM) polymerisation of monomers containing two cyclopentene moieties **1.80** followed by modification via insertion polymerisation (**Scheme 1.18**).^[54] Firstly, ROM/RCM was used to yield well defined polymers **1.81** with no evidence of cross linking or depolymerisation. Coupling of polymer

1.81 with diacrylate **1.85** yielded an A,B-alternating copolymer **1.86**. Furthermore, they showed that these two sequential processes could actually be done in a one-shot process; multiple olefin metathesis polymerisation (MOMP), a combination of ROM/RCM/CM. Initial focus on the ROM/RCM of dicyclopentene **1.80** found that dilute concentration of 0.1 M led to successful polymerisation to yield poly(2,5-disubstituted-2,5-dihydrofuran) **1.81** as a soluble polymer, however increasing the concentration to 1.0 M led to an insoluble gel after 10 mins. This is likely due to the high concentrations allowing for the ROMP to dominate, resulting in a cross linked network. The critical monomer concentration, $[M]_c$ of a ROMP is the concentration below which the cyclic monomer predominates, and above which linear chains emerge.^[55] Cyclopentene **1.80** has an $[M]_c$ of 0.8 M at 25 °C, therefore it is expected that above this concentration, the ROMP to form **1.81** will dominate, and below which either no polymerisation will occur, or ROM/RCM will take over. Indeed Grubbs *et al.* showed that at 0.5 M the ROM/RCM of dicyclopentene **1.80** resulted in full conversion to soluble polymer with a dispersity of 1.79. Interestingly, ROMP of dicyclopentene **1.80** at 1.0 M to yield the cross linked gel followed by dilution to 0.5 M, resulted in the dissolution of the polymer after 6 h. This was possible as the dilution led to the decross-linking via the intra-molecular ROM/RCM to yield soluble polymer.

Synthesis of the A,B-alternating copolymer **1.86** was then investigated. It was found that coupling of poly(2,5-disubstituted-2,5-dihydrofuran) **1.81** with diacrylate **1.85** could be achieved with the use of **HG2** without disturbing the cyclic olefin of the polymer backbone, to produce copolymer with dispersity of 2.09. Furthermore, a one-shot polymerisation was achieved by the ROM/RCM/CM of dicyclopentene **1.80** and diacrylate **1.85** to yield copolymer **1.86** with dispersity 2.11. This was the first reported synthesis by multiple olefin metathesis polymerisation (MOMP).

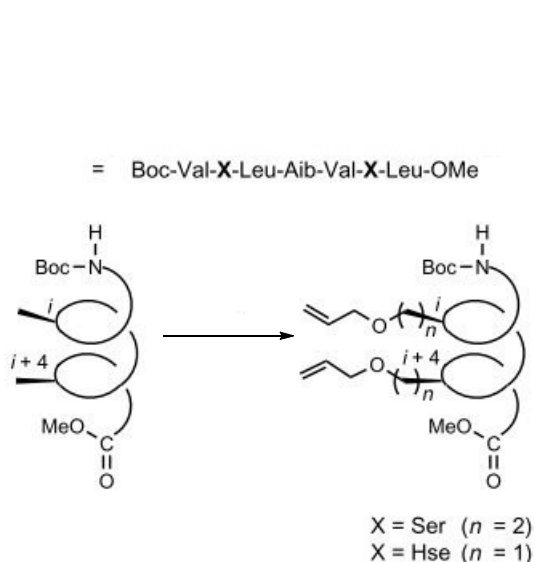
1.5 Post-polymerisation Modification Reactions

Polymers with appropriate functionalisation are vital to the application of the polymer, however the synthesis of pertinent and useful polymers frequently require post-polymerisation modification via a grafting-onto approach in order to incorporate functionality that is not compatible with the polymerisation process.^[56] Pre-functionalised monomers could potentially be protected prior to polymerisation, however due to the added step of deprotection and, most importantly, purification, this is often an undesirable option. As a result, many chemists opt for a post-polymerisation method. Additionally, some architecture can only be installed as a post-polymerisation modification, such as cross-linking.^[57]

With respect to side-chain functionalisation with small molecules, this is commonly achieved by employing azide-alkyne cycloaddition,^[58] terminal functional group modification,^[59] thiol-ene addition,^[60] Michael-type addition,^[61] and amidation.^[62] Recently, there has been a focus on using olefin cross metathesis to functionalise polymers.^[63–65]

1.5.1 Olefin Cross Metathesis on polymers

Initial use of olefin metathesis to modify polymers was first investigated in 1998 by Grubbs *et al.* with the synthesis of covalently linked peptide helices using RCM.^[66] Acyclic dienes were incorporated into the linear peptide sequence of heptapeptide (Scheme 1.19). These allylic ethers were installed at the i and $i + 4$ positions, as it was believed that these positions would be close to each other in space in the final helical structure. Treatment of 20 mol% of **G1** resulted in the RCM of pendent olefins in 90% yield ($n = 1$), and $E:Z$ selectivity of 5:1.



Scheme 1.19 - Diene analogues of heptapeptides^[66]

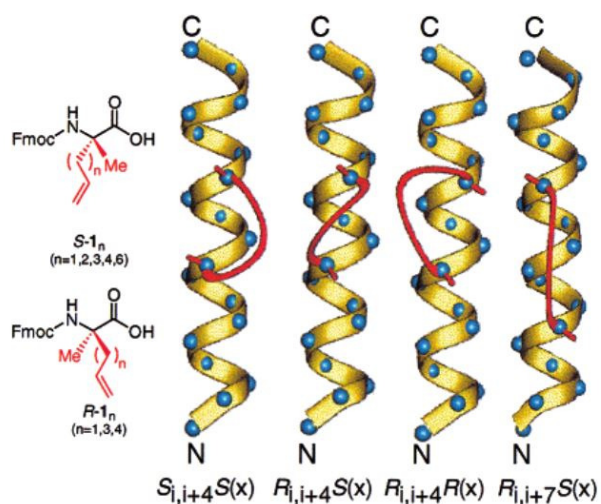


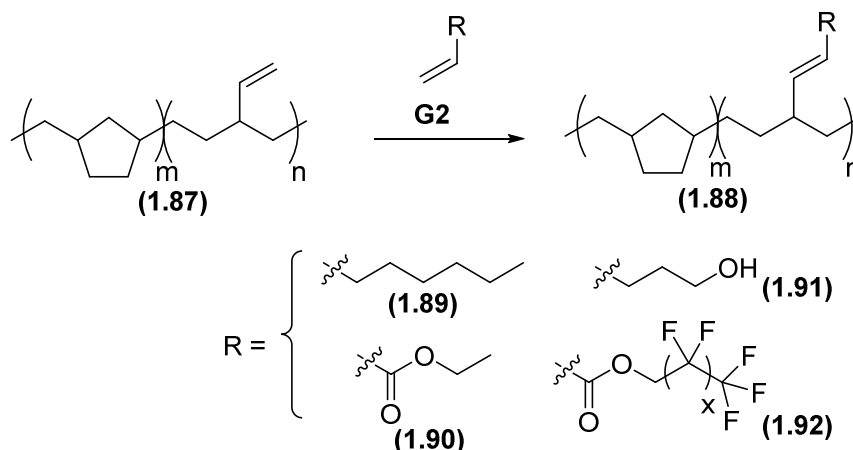
Figure 1.6 - Stabilizing α -helices by CM of unnatural amino acids^[67]

In 2000, Verdine *et al.* built upon this work by incorporating various S and R configured α -allyl amino acids within the peptide sequence prior to CM.^[67] The match/mismatch use of these S and R unnatural amino acids at the i and $i + 4$ positions allowed for the successful stabilisation of the helical structure as determined by circular dichroism spectroscopy (**Figure 1.6**). In particular optimal stabilisation was achieved using $R_{i,i+7}S(11)$, which corresponded to a peptide with an R and an S configured amino acid at positions “ i ”, and “ $i+7$ ” respectively, and 11 carbons in the metathesised cross-link.

In 2007, Coates *et al.* reported the synthesis of nanoparticles by crosslinking linear polymers using CM.^[68] Polycarbonate possessing pendent vinyl groups were synthesised by living polymerisation to yield polymers in narrow dispersity ($\mathcal{D} = 1.20$) with $M_n = 54,100$ g.mol⁻¹. Treatment with **G2** at high concentrations led to crosslinking and large increase in dispersity indicating that intermolecular cross linking was prevalent. However, under dilute

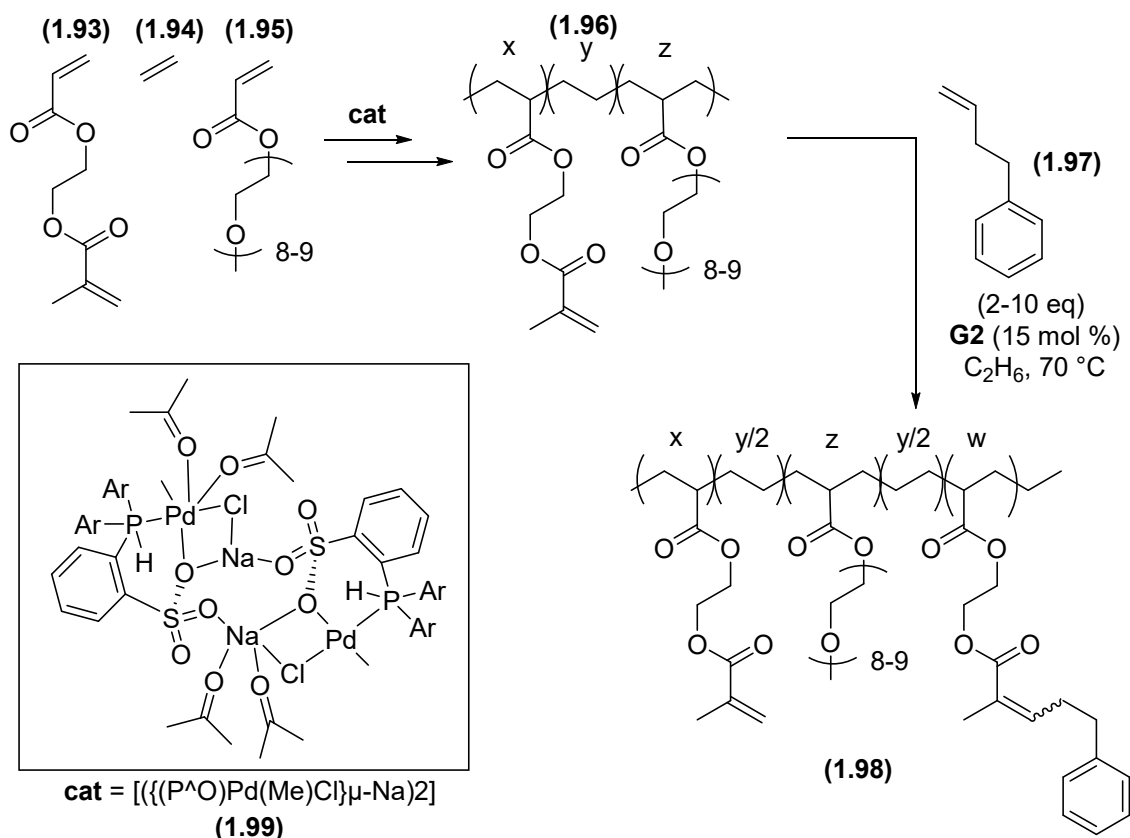
conditions (1 mg/mL), CM occurred with the retention of a narrow dispersity, indicating the absence of intermolecular CM, to yield nanoparticles that were observable by atomic force microscopy (AFM).

The use of olefin cross metathesis to couple small molecules to polymers is a relatively new field, with only a handful of articles tackling this area. In 2004, Coates used CM to couple type 1 and type 2 alkenes with various polyolefins possessing pendent vinyl groups **1.87** (Scheme 1.20).^[69] This was accomplished without considerable increases in dispersity indicating that self-metathesis was subdued. Conversion rates varied between 45% and 91% even when 10 equivalents of coupling partner were used.



Scheme 1.20 - CM on polyolefins using G2 catalyst by Coates et al.^[69]

In 2010, Mecking *et al.* reported the coupling of 4-phenylbutene **1.97** to poly(ethylene-co-AAEM-co-APEG) **1.96** (AAEM = 2-(methacryloyloxy)ethyl acetoacetate, APEG = oligoglycol monoacrylate).^[70] Catalytic insertion polymerisation was accomplished using dimeric compound $[\{(\text{P}^{\wedge}\text{O})\text{Pd}(\text{Me})\text{Cl}\}\mu\text{-Na}\}_2]$ **1.99**, which is selective for the unhindered acrylate region of AAEM **1.93**, leaving the methylacrylate moiety intact and available for post-polymerisation modification (Scheme 1.21). Subsequent CM with 4-phenylbutene **1.97** using **G2** allowed for successful conjugation. Unfortunately, this was not accomplished in quantitative yield, likely due to the pendent olefin of polymer **1.96** being an electron poor gem-disubstituted alkene, and therefore relatively unreactive to CM.



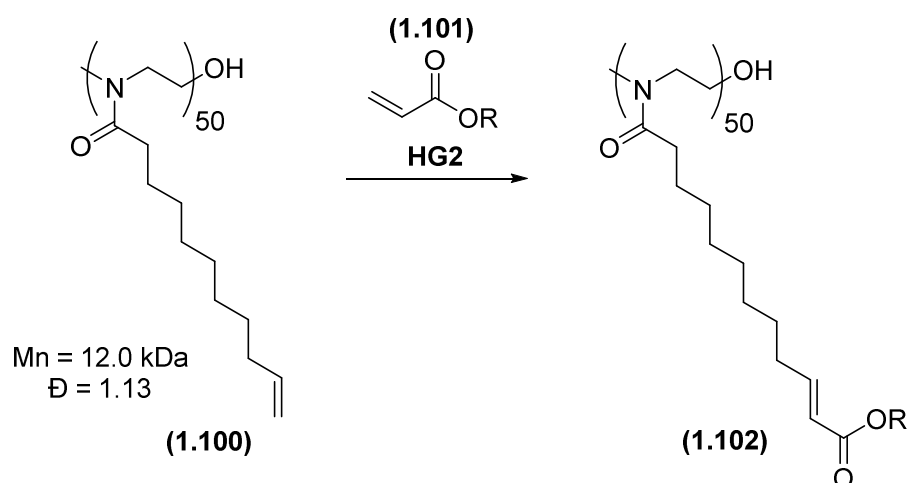
Scheme 1.21 - CM of 4-phenylbutene with poly(ethylene-co-AAEM-co-APEG).

In 2012, Hoogenboom and Meier *et al.* showed that a range of acrylate moieties could successfully be coupled to 10-undecenoic acid derived poly(2-oxazoline) **1.100** (Scheme 1.22).^[63] Previous work by Hoogenboom *et al.* had achieved the synthesis of poly(2-(dec-9-enyl)-2-oxazoline) (PDecEnOx) **1.100** by cationic ROP of the unsaturated fatty acid based monomer.^[71] The pendent terminal alkenes were then subjected to CM with various acrylates (Table 1.3). This was done with good success however the occurrence of self metathesis (SM) was observed, which is the process by which the pendent olefins of the polymer undergoes CM with another pendent olefin either intramolecularly (to yield cyclic structures), or intermolecularly (resulting in cross linking). This homodimerisation occurs due to the unhindered nature of the pendent olefin, allowing for the ruthenium catalyst to easily access the alkene.

Investigation into the reaction conditions was carried out focussing on reaction concentration, temperature and the number of equivalents of the acrylate coupling partner. It was hypothesised that a decrease in concentration would keep the pendent alkenes far away from each other thereby lowering the occurrence of intermolecular SM, however this may also reduce the catalytic activity resulting in lower successful conjugation with the acrylate. Interestingly, a concentration of 0.6 M was suggested to be optimal to achieve low SM and high conversion. No discussion was made to why this relatively high concentration is necessary, however we speculate that this increase in concentration helps to drive

successful conjugation in the early stages of the reaction, which then acts as steric hindrance to subsequent SM. Overall, this undesired homodimerisation process was limited by using a high number of equivalents of the type 2 acrylate coupling partner with **HG2** in dichloromethane at 40 °C.^[53]

Investigation of coupling partner found that an increase in the size of the acrylates led to a decrease in intermolecular SM. The group propose the reason for this may be that once the acrylate is attached, the large steric bulk results in significant hindrance around the polymer backbone, thereby preventing adjacent pendent olefins from undergoing CM with other polymer strands.



Scheme 1.22 - CM of poly(2-oxazoline) with acrylate

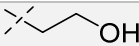

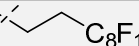
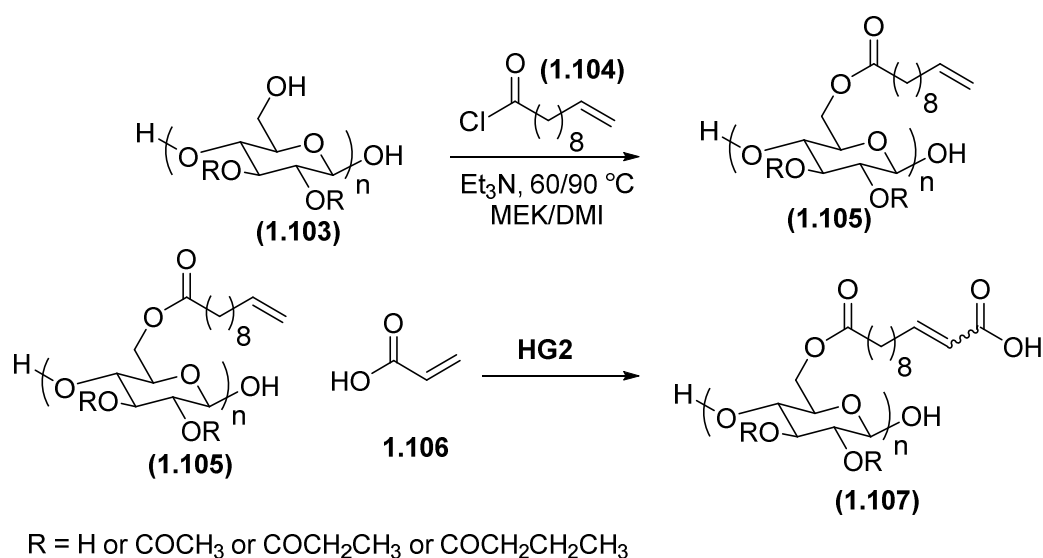
R	Yield (%)	M_n (kDa)^a	Đ^a
Me	92	15.7	1.33
Et	89	16.4	1.32
Bu	84	17.3	1.27
Hex	72	18.1	1.15
	80	16.6	1.21
	87	23.6	1.19
	60	20.7	1.14
<i>t</i> -Bu	87	18.3	1.23

Table 1.3 - CM of PDecEnOx with various acrylates ^a analysed by GPC

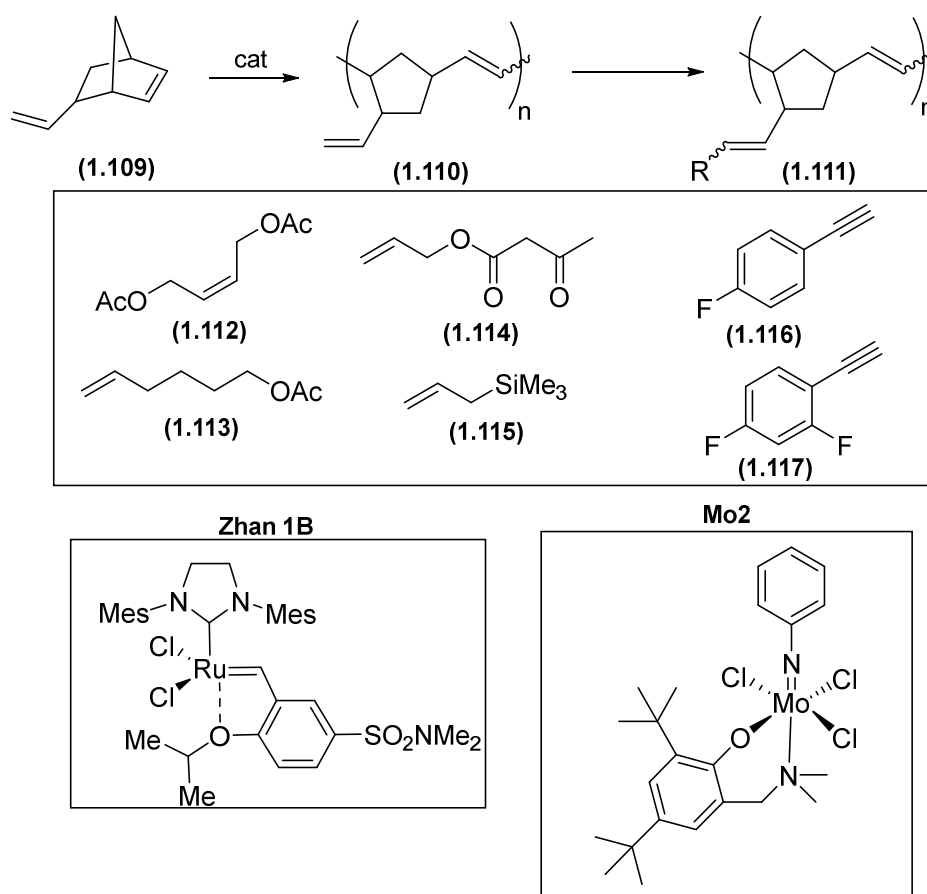
In 2014, Edgar *et al.* studied the modification of polysaccharides by CM to synthesise cellulose ω -carboxyalkanoates **1.107**.^[72] The olefin handle was first grafted onto the primary alcohol of polysaccharides **1.103** with 10-undecenoyl chloride **1.104** (Scheme 1.23). These terminal alkenes were then conjugated with acrylic acid using **HG2** catalyst. Use of acrylic acid as a solvent yielded 100% conversion, however when solvents of DCM or THF were used, the product attained only 90% conversion and appeared to undergo gelation, which is thought to be the product of cross-linking. Edgar *et al.* then built upon this work by using CM to synthesise hydroxypropyl cellulose.^[73]



Scheme 1.23 - Modification of polysaccharides using CM.

The substrate scope for polymer functionalisation by CM has recently been extended beyond acrylate coupling partners. In 2014, Balcar *et al.* reported the ROMP of vinylnorbornene (VNBE) **1.109** followed by successful conjugation with a variety of type 1 coupling partners. ROMP of VNBE was performed with catalysts of i) Hoveyda-Grubbs type complex (**Zhan 1B**), and (ii) molybdenum (VI) complex **Mo2** with a bidentate aminophenolate ligand (**Scheme 1.24**). The synthesised polymer **1.110** possessed M_n in the range of 10,000 to 13,000 g.mol⁻¹. In the case of **Mo2**, the dispersity of the polymer was 3.2. Pendent vinyl groups were found to remain intact, which is due to the **Mo2** catalyst being specific for ROMP over CM.^[74] However, use of **Zhan-1B** resulted in dispersity values ranging from 4.6 to 8.5. This increase in dispersity is likely due to the less selective Ru based catalyst being able to react with the pendent vinyl groups, resulting in branching/cross linking.^[75] Post-polymerisation modification of **1.110** via CM reactions of pendent vinyl groups was carried out with the **Zhan-1B** catalyst. Functionalised soluble polymers of M_n from 6,000 to 23,000 g.mol⁻¹ were prepared. A decrease in M_n may be due to the depolymerisation of the unsaturated polymer backbone. Functionalisation of PVNBE

via CM of pendent vinyl groups was accomplished with partners **1.112-1.117**, with the best results observed with *cis*-1,4-diacetoxybut-2-ene **1.112** (59% conversion). Diacetoxybut-2-ene is essentially the homodimer of allyl acetate, and it has been reported by Grubbs *et al.* that use of the preformed homodimer in a CM coupling often affords better results than the non-homodimerised coupling partner.^[76] This difference in yield is likely due to the rapid homodimerisation of the type 1 allyl acetate dominating the catalytic cycle, resulting in the increased formation of a less stable ruthenium methylidene species.^[77] By extension, this may be the reason that lower conversions were obtained for the nondimerised coupling partners: 5-hexenyl acetate **1.113**, allyl acetoacetate **1.114**, and allyltrimethylsilane **1.115** (30%, 11% and 6% respectively). Dispersity remained relatively constant with all coupling partners, except in the case of allyltrimethylsilane **1.115**, where a dispersity value of 32 was reported. Functionalisation of PVNBE was also performed via ene-yne cross-metathesis of pendent vinyl groups with (4-fluorophenyl) acetylene **1.116** and (2,4-difluorophenyl)acetylene **1.117**, achieving 23% and 35% conversion respectively. Overall, Balcar *et al.* expanded the scope of post-polymerisation modification by CM, however in the case of PVNBE, extensive polymer degradation was observed in many cases.



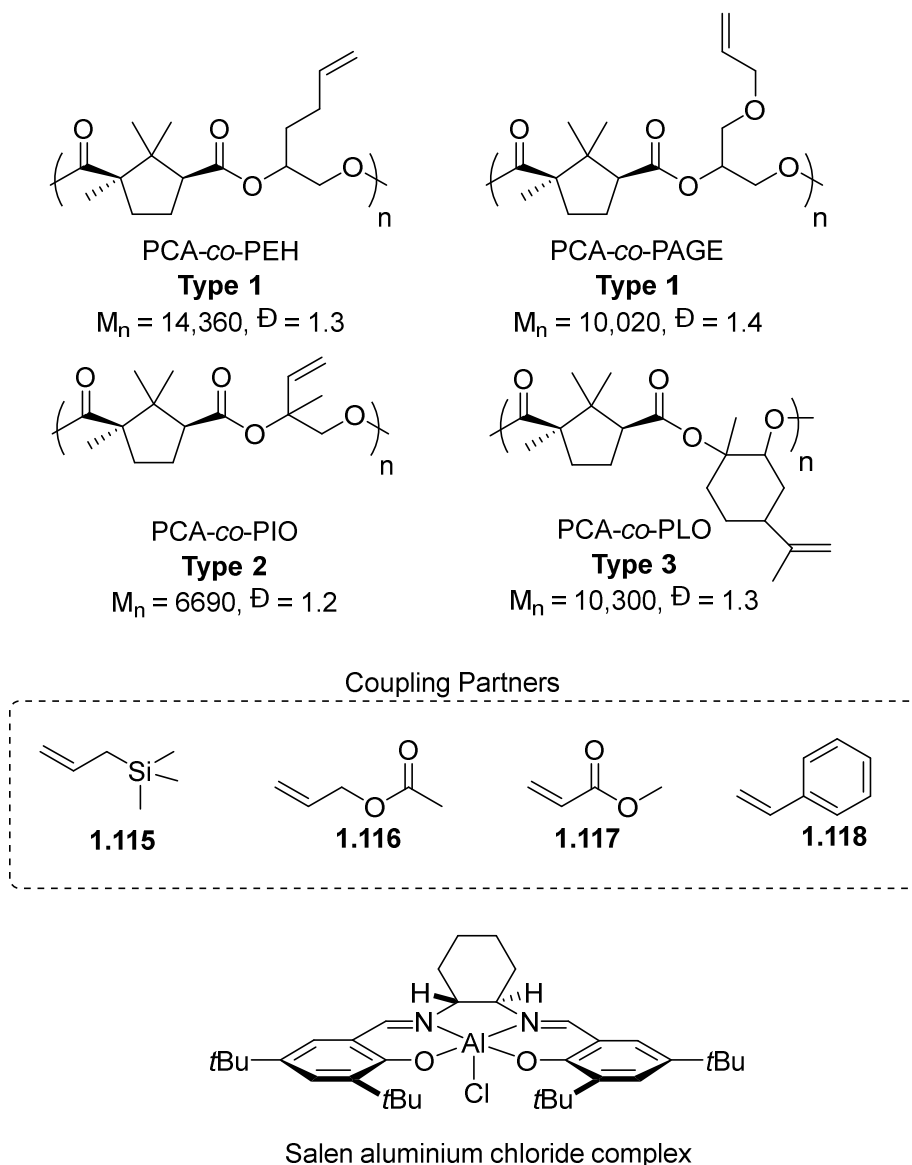
Scheme 1.24 – ROMP of VNBE and subsequent functionalisation.

Work by Prunet and Thomas *et al.* in 2016 studied the functionalisation of pendent allyl groups of aliphatic polyesters by CM (**Scheme 1.25**).^[64] Synthesis of copolymers were

achieved by the tandem catalysis of camphoric anhydride (CA) with various epoxides using salen aluminum chloride complex and [PPN]Cl ([PPN] = bis(triphenylphosphoranylidene)iminium) as a co-catalyst.^[78] This resulted in polyesters of $M_n \approx 10,000 \text{ g.mol}^{-1}$ and $\bar{D} \approx 1.3$. Both PCA-co-PEH and PCA-co-PAGE are type 1 in nature, and so may result in rapid self-metathesis. The more hindered olefin of PCA-co-PIO means that this type 2 alkene may be less prone to homodimerisation. Gem-disubstituted PCA-co-PLO is a type 3 olefin, which may result in an inability to undergo successful CM, although there should be no possibility of self-metathesis.

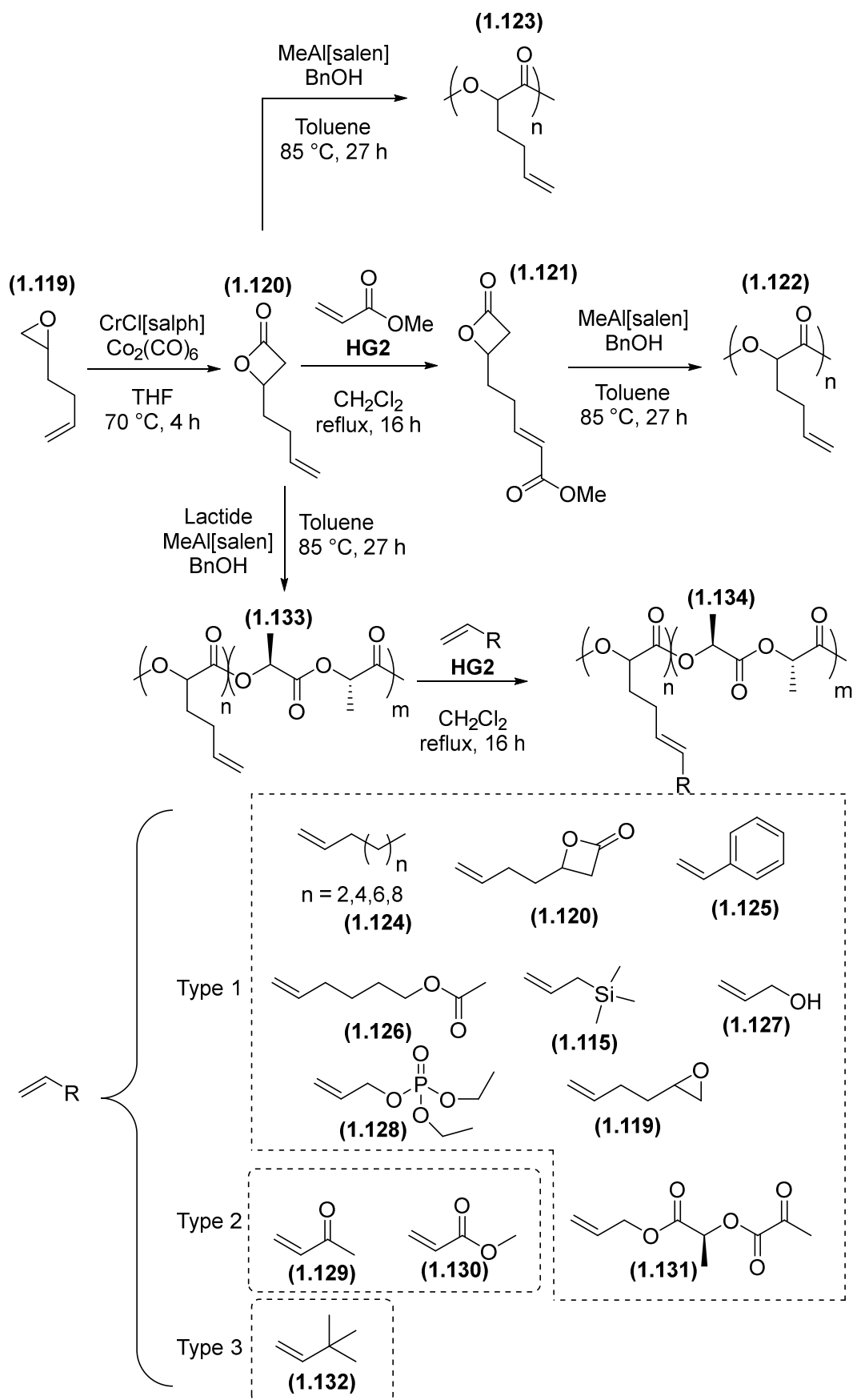
Investigation with the coupling of type 1 polymers, PCA-co-PEH and PCA-co-PAGE with methyl acrylate allowed for good conversion (93 and 98% respectively). There was no evident self metathesis as observed by NMR, and dispersity values remained constant. Interestingly, this coupling with methyl acrylate only resulted in a marginal increase in M_n compared to their parent polymers as observed by GPC, which the authors propose is due to a small change in hydrodynamic volume of the functionalised polymers. Type 2 and 3 polymers, PCA-co-PIO and PCA-co-PLO, only led to trace amounts of coupling. PCA-co-PAGE was then subjected to CM with allyl trimethylsilane, styrene and allyl acetate, and in each case conversion >90% was achieved, with little change in dispersity.

In general it was found that PCA-co-PAGE was the best candidate for post-polymerisation modification by CM. Methyl acrylate was an optimal coupling partner when **HG2** was used at 15 mol% loading.^[64] Notably PCA-co-PAGE showed no evidence of self metathesis, even when the polymer was stirred with **HG2** in the absence of a coupling partner, which is surprising considering the type 1 nature of the terminal olefin. However, self metathesis is possibly subdued due to the cyclopentene containing backbone of PCA-co-PAGE being more rigid in nature than the linear polymers e.g. poly(2-oxazoline) synthesised by Hoogenboom/Meier. This rigidity would especially prevent intramolecular cyclisation by RCM.



Scheme 1.25 - Structures of various polyesters synthesised with aluminium complex catalyst.

Recently Shaver *et al.* have used olefin metathesis to synthesise various functionalised biodegradable poly(hydroxyalkanoate)s (Scheme 1.26).^[65] This was achieved by both pre and post-polymerisation functionalisation of β -heptenolactone (β H_L) **1.120**. The lactone monomer **1.120** was first synthesised by carbonylation of 1,2-epoxy-5-hexene **1.119** using [salph(Cr(THF)₂)] [Co(CO)₄] catalyst. In the pre-polymerisation modification, lactone **1.120** was subjected to CM with methyl acrylate to yield the monomer **1.121** that was then subjected to ROP using aluminium salen catalyst. This resulted in polymerisation with 93% conversion, however molecular weight of **1.122** was low ($M_n = 4,200 \text{ g.mol}^{-1}$), below the target of $M_n = 18,400 \text{ g.mol}^{-1}$. Additionally the dispersity was relatively high, $\bar{D} = 1.65$, and it was proposed that the acrylate species coordinates to the Lewis acid aluminium centre, resulting in suppressed control of the polymerisation.



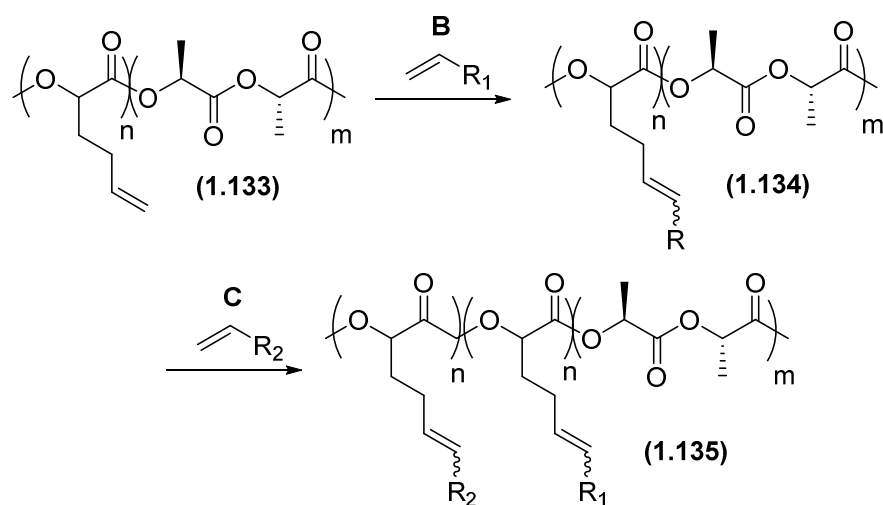
Scheme 1.26 – Polymerisation and modification of polyesters by Shaver *et al.*^[65]

In the post-polymerisation method, the lactone monomer **1.120** underwent ROP with Al(salen) catalyst to yield polyester **1.123** possessing pendent terminal olefins ($M_n = 12,100$ g.mol⁻¹, $\bar{D} = 1.09$) Coupling with methyl acrylate allowed for 99% conversion, however only a marginal increase in M_n was recorded by GPC ($M_n = 13,400$ g.mol⁻¹, $\bar{D} = 1.84$). This marginal change in M_n after CM was a similar effect to that observed by Prunet and Thomas *et al.*^[64] The increase in dispersity indicates the occurrence of self metathesis, which is unsurprising considering the type 1 nature of the pendent olefins. Additionally, when polyester **1.123** was subjected to CM in the absence of coupling partner, extensive cross-linking occurred to yield an insoluble gel.

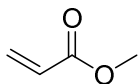
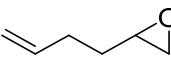
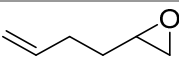
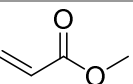
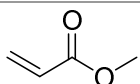
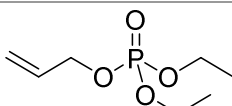
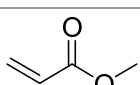
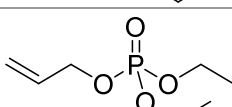
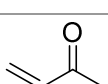
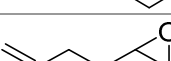
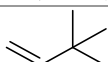
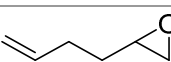
Copolymerisation of lactone **1.120** with renewable and inexpensive lactide was then performed to produce copolymer **1.133**. Due to the high rate of polymerisation of lactide compared to lactone **1.120**, a gradient copolymer was produced ($M_n = 12,000$ g.mol⁻¹, $\bar{D} = 1.02$). An extensive substrate scope for CM was then investigated including a range of type 1-3 olefins. In general, type 2 and 3 coupling partners yielded full conversion with good retention of dispersity. Other type 1 species yielded lower conversion, likely due to the rapid homodimerisation pathway dominating catalytic cycle. The group did isolate the polymers that did not go to full completion, and resubmit them to CM, however only **1.124** ($n=2$) and **1.119** resulted in full conversion after the second round of CM. The remaining polymers retained between 10-40% of the parent alkene. Shaver *et al.* propose that the rate of successful CM between the polymer and the coupling partner is in competition with the rate of homodimerisation of the coupling partner.^[79] However we propose that, in addition to this, the rapid homodimerisation of the type 1 coupling partner may be leading to less stable ruthenium methyldiene species that leads to degradation of **HG2** as reported by Grubbs *et al.*^[77] It would be interesting to repeat these coupling reactions with the preformed dimers of the type 1 coupling partners.

The group also performed double CM, where the conjugated polymer from the first CM coupling was subjected to a second CM reaction with a different partner. (**Scheme 1.27**). The general approach to this was to start with the CM of **1.133** with a type 2 or 3 species and, as the coupling approaches completion, add a more reactive type 1 partner (Table 1.4). It was observed that the order of the CM is crucial to obtaining a dual functionalised polymer **1.135**. Addition of methacrylate first followed by secondary CM with epoxide **1.119** allowed for incorporation of both coupling partners in roughly equal proportions. However reversing the order of addition resulted in solely conjugation of the polymer to methyl acrylate. Shaver *et al.* propose that rate of secondary metathesis of the functionalised polymer bearing methyl acrylate is slower than the rate of homodimerization of epoxide **1.119**.^[79] Coupling of type 3 olefin **1.132** followed by secondary CM with epoxide **1.119** yielded no incorporation of the epoxide into the polymer. This indicates that the alkene that

results from the coupling of the type 3 species is unreactive to CM, and therefore type 4 in nature as it is unable to undergo secondary metathesis with the epoxide **1.119**.



Scheme 1.27 – Double CM of copolymer^[65]

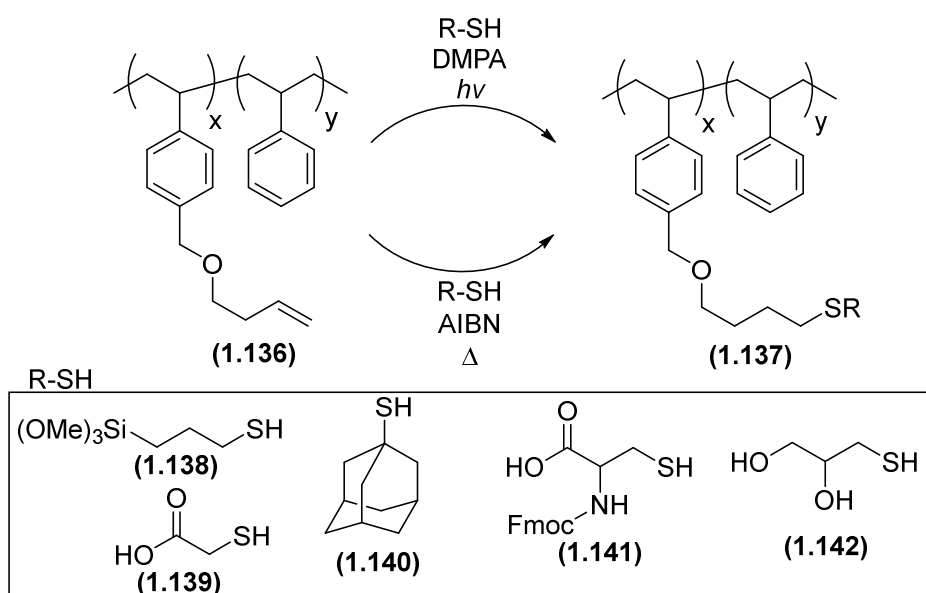
B	Eq	% of 1.133 remaining	C	Eq	A:B:C
	1	13		8	0:1:0.78
	12	13		5	0:0:1
	1	18		5	0:0.36:1
	8	0		0.3	0:1:0.25
	8	6		0.3	0.26:0.9:1
	8	0		0.3	0:1:0
Table 1.4 - Double CM of copolymer					

In conclusion, CM is a relatively unexplored method of functionalising polymers, even though it has the added benefit over many click-reactions of retaining the olefin moiety that could be utilised to achieve further functionalisation. Unfortunately, a common problem for some polymers undergoing CM is the propensity to yield a self-metathesis product. This can lead to an increase in polymer dispersity, which can be detrimental for drug delivery

applications. Additionally, no research has yet been published on the use of CM on polyethers; a family of polymers widely used in medical applications.

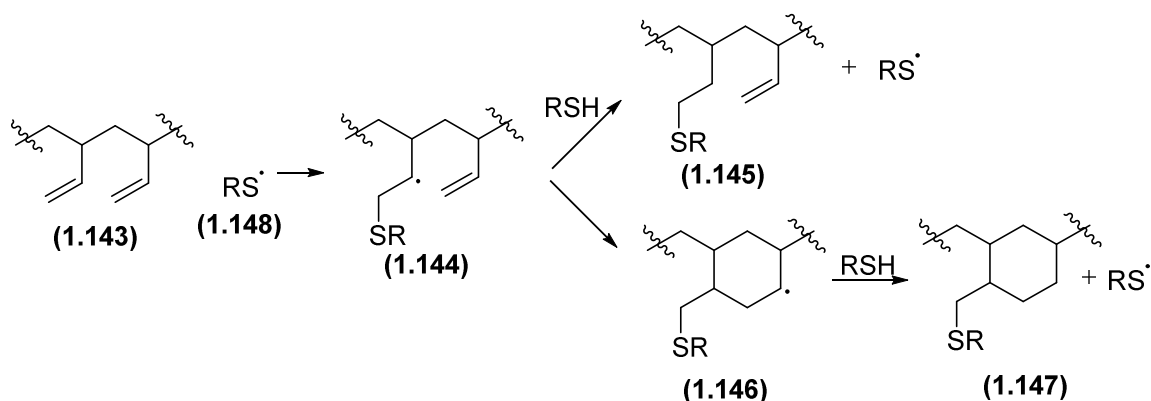
1.5.2 Thiol-Ene Addition on polymers

As discussed previously, the use of the thio-ene addition reaction to achieve polymer modification was first described in the vulcanisation of poly(cis-isoprene). This radical-mediated addition is what is commonly referred to as thio-ene addition, however the process can also occur by nucleophilic attack of an olefin by anionic sulfur in a Michael-type addition. The radical mediated pathway can be initiated either thermally or photochemically. Hawker *et al.* have shown that both of these pathways are possible in order to achieve full conversion of pendent olefins of **1.136** with various thiols **1.138-1.142**, however photochemical induction offered the advantage of milder reaction conditions and shorter reactions times (**Scheme 1.28**).^[80]



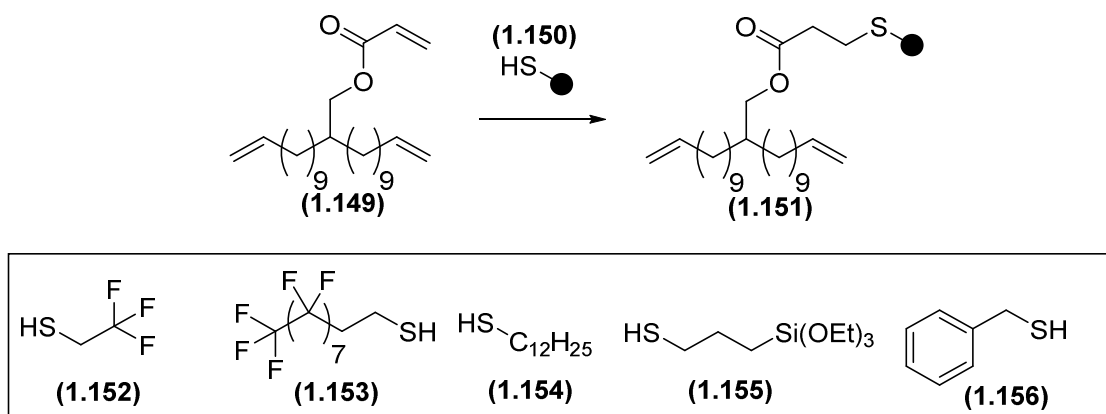
Scheme 1.28 - Thiol-ene addition - Hawker *et al.*^[80]

Schlaad *et al.* have reported that use of thiol-ene addition to pendent olefins of 1,2-polybutadiene **1.143** can be problematic due to the formation of the anti-Markovnikov radical **1.144**, formed upon conjugation with radical sulphur **1.148**, to undergo cyclisation with an adjacent alkene to yield **1.146** (**Scheme 1.29**).^[81] However this process can be limited by increasing the concentration of thiol and decreasing the temperature.^[82] Additionally increasing the distance of the pendent olefins from the polymer backbone has been proven to be a good way to limit this radical cyclisation.^[83]



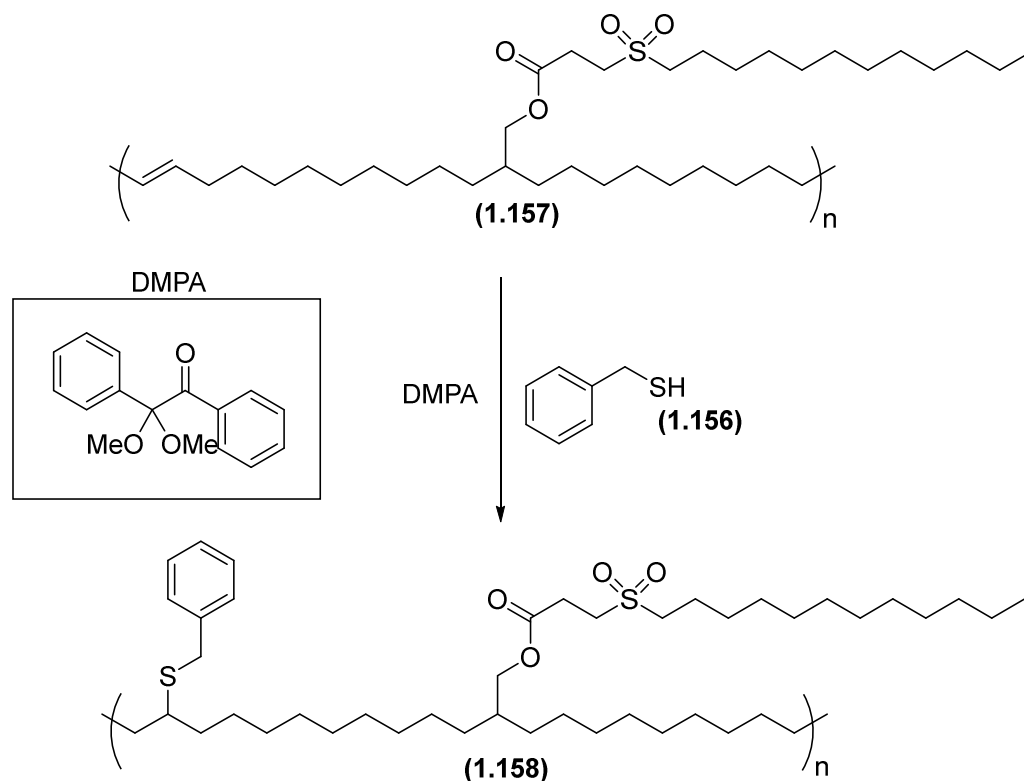
Scheme 1.29 - Potential radical reaction pathways of the addition of mercaptans onto the vinyl double bonds of 1,2-polybutadiene by Schlaad et al.^[81]

Lowe *et al.* have used a combination of thiol-ene addition in both a radical and Michael fashion to synthesise novel polymers via acyclic diene metathesis (ADMET) polymerisation.^[84] Starting with the synthesis of the α,ω -diene, 2-(undec-10-en-1-yl)tridec-12-en-1-yl **1.149**, followed by the chemoselective Michael-type addition of thiol **1.150** with the electron poor acrylate, to furnish a range of monomers. (Scheme 1.30).



Scheme 1.30 - Monomer synthesis by Michael type thiol-ene addition by Lowe et al.^[84]

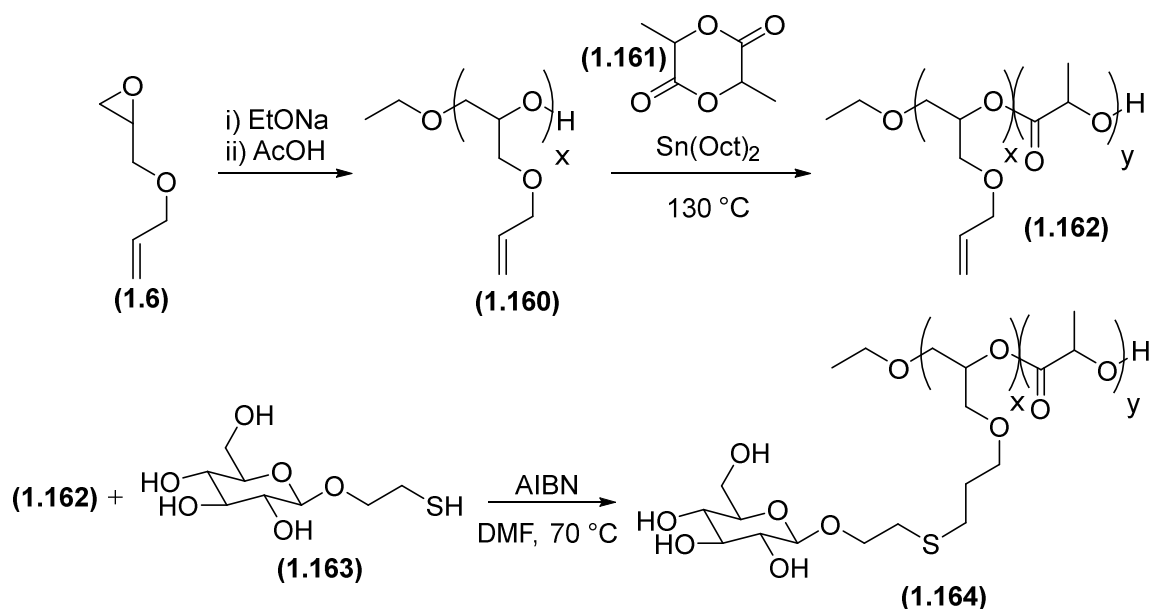
Subsequent ROMP of the electron rich alkenes using **G1** was not possible due to the strong coordination strength of sulphur for ruthenium, however after oxidation of the thio-ether **1.151** to the sulfoxide-sulfone **1.157** using triazotriphosphorine tetrachloride (TAPC), the polymerisation was achieved in high conversion. The thiol-ene reaction was then employed in a radical fashion to further functionalise backbone of polymer **1.157** at the unsaturated positions (Scheme 1.31). This example nicely highlights the possible incompatibilities between two functionalisation methods, and so attention must be paid to the order in which functionalisations are conducted.



Scheme 1.31 - Radical thiol-ene addition to alkene groups on the polymer backbone by Lowe et al.

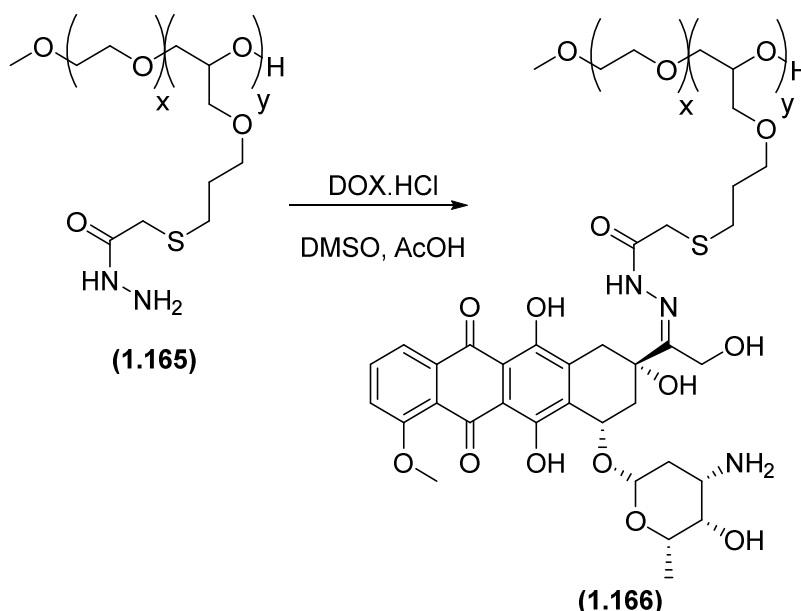
PAGE Functionalisation by thiol-ene click

Hu *et al.* functionalised PAGE-*b*-PLA **1.162** with glucose species **1.163** using thiol-ene click chemistry.^[85] The group polymerised AGE **1.6** using sodium ethoxide initiator to yield PAGE **1.160** with controlled, yet low M_w (2000 – 4000 g.mol⁻¹) and good dispersity (\mathcal{D} = 1.04 – 1.08) (**Scheme 1.32**). This monohydroxyl polymer **1.160** was then used as a macroinitiator in the ROP of lactide **1.161**. This block copolymer **1.162** was functionalised using 2-mercaptoethyl- β -glucoside **1.163** via radical thiol-ene addition, which was achieved with full conversion. These amphiphilic glycopolymers **1.164** were then able to undergo self-assembly into core-shell micelles with a glucose outer coating, which could potentially be used in polymeric micelles for drug delivery.



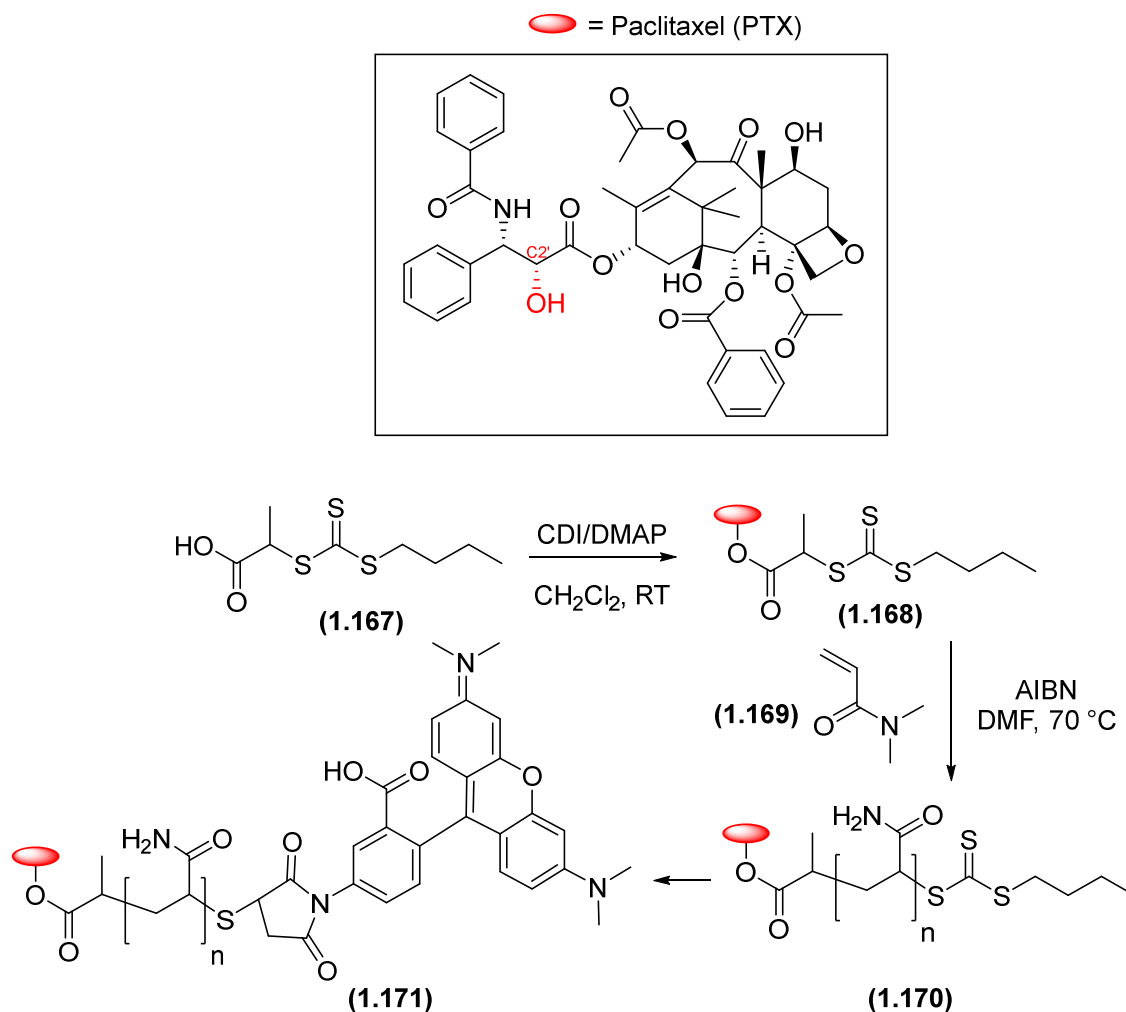
Scheme 1.32 – Synthesis of P(AGE-glucose)-b-PLA.

Hrubý et al.^[86,87] studied the development of a micellar pH-sensitive system for the drug delivery of the antibiotic doxorubicin (DOX). This polymer micelle created from poly(ethylene oxide)-*block*-poly(allyl glycidyl ether) PEO-*b*-PAGE, which had undergone radical thiol-ene with methyl sulfanylacetate. The pendent ester was then converted to the hydrazide **1.165** using hydrazine hydrate. This was then coupled with the DOX to yield the pH sensitive hydrazone **1.166** (**Scheme 1.33**). This drug-polymer conjugate was then treated with either aqueous buffers at pH 5.0 (simulating the pH in endosomes) or pH 7.4 (pH of blood plasma). The group were able to show that doxorubicin was released much faster at pH 5.0 compared to pH 7.4.



Scheme 1.33 – Synthesis of DOX hydrazone

An interesting use of thiol-ene chemistry has been demonstrated by Geest *et al.* when synthesising a prodrug of paclitaxel-polymer by grafting the polymer from the drug itself.^[25] This is especially interesting because it concerns paclitaxel (PTX); a widely used anticancer drug that has been conjugated to a variety of macromolecules with the aim of improving the drug's pharmacokinetic properties, namely solubility. This synthesis began with esterification of (2-(butylthiocarbonothioylthio)propanoic acid (PABTC) **1.167** with PTX at the C2' position to yield the paclitaxel-chain transfer agent (PTX-CTA) **1.168**. RAFT polymerisation of this CTA with *N,N*-dimethylacrylamide **1.169** led to polymer **1.170** in low dispersity, possessing a terminal trithiocarbonate, which could undergo aminolysis to the thiol (**Scheme 1.34**). Thiol-ene addition to tetramethylrhodamine (Rho) maleimide was then conducted to yield a fluorescently tagged paclitaxel-polymer conjugate **1.171**. Although this is an example of an end-group modification as opposed to side-chain modification, it nicely exemplifies one of the possible uses of the CTA trithiocarbonate after RAFT polymerisation has been complete.



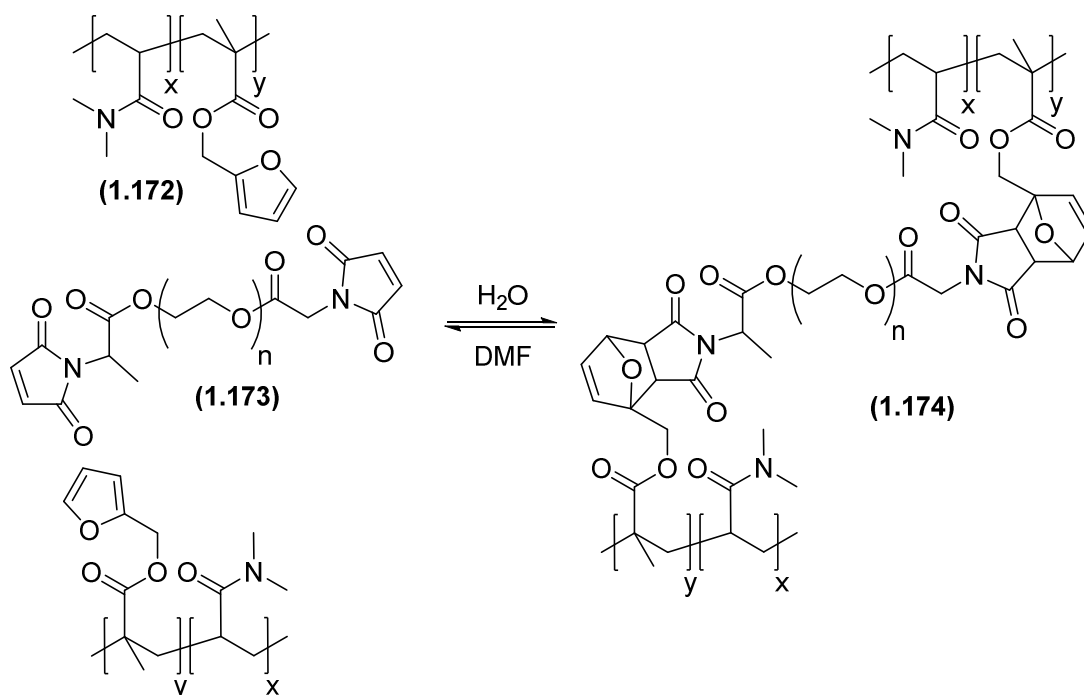
Scheme 1.34 - Synthesis of paclitaxel-polymer conjugate by RAFT of drug-CTA precursor, followed by thiol-ene addition to fluorescent maleimide by Geest *et al.*^[25]

1.5.1 Diels-Alder reaction on polymers

Diels-Alder reaction is an attractive method to functionalise polymers as it can often be achieved quantitatively with no side products, whilst being compatible with a wide range of functional groups.^[88] The most widely used precursors to polymer functionalisation by the Diels-Alder reaction are furan (diene) and maleimide (dienophile) to yield an oxabicyclic.^[89] Upon heating, this Diels-Alder adduct can revert back to the diene and dienophile. This is a property that has been utilised to develop thermoresponsive materials in the form of gels, dendrimers and smart copolymers.^[90,91]

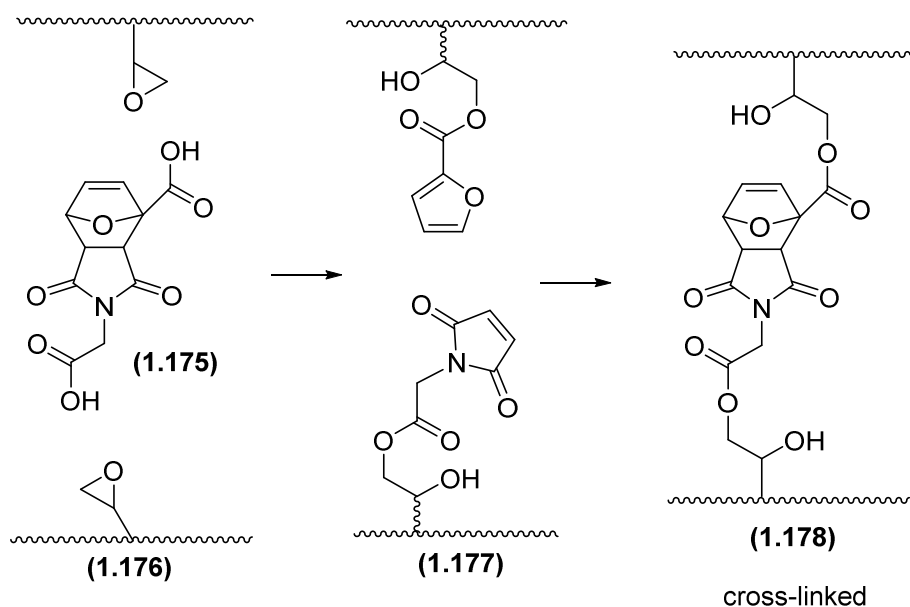
Work by Wei *et al.* has focused on the use of the Diels-Alder reaction to create thermoresponsive hydrogels.^[90] These were synthesised in aqueous conditions by a Diels-Alder reaction of poly(*N,N*-dimethylacrylamide-*co*-furfuryl methacrylate) (PDMAFM) **1.172** and *N*-[4-(formyl polyethylene glycol ester)] bismaleimide **1.173**, resulting in cross linked

architecture **1.174**. It was found that aqueous media could accelerate the Diels-Alder reaction, whereas DMF could accelerate the *retro*-Diels-Alder reaction, thereby controlling disassembly of the hydrogel (**Scheme 1.35**). Interestingly these hydrogels were stable in hot water,^[91] with an increase in temperature leading to a decrease in gelation time. The group have also increased the biocompatibility of these hydrogels by using a dienophile terminated PEG in place of bismaleimide **1.173**.^[90]



Scheme 1.35 - Hydrogels formed by the Diels-Alder reaction – Wei et al.^[90]

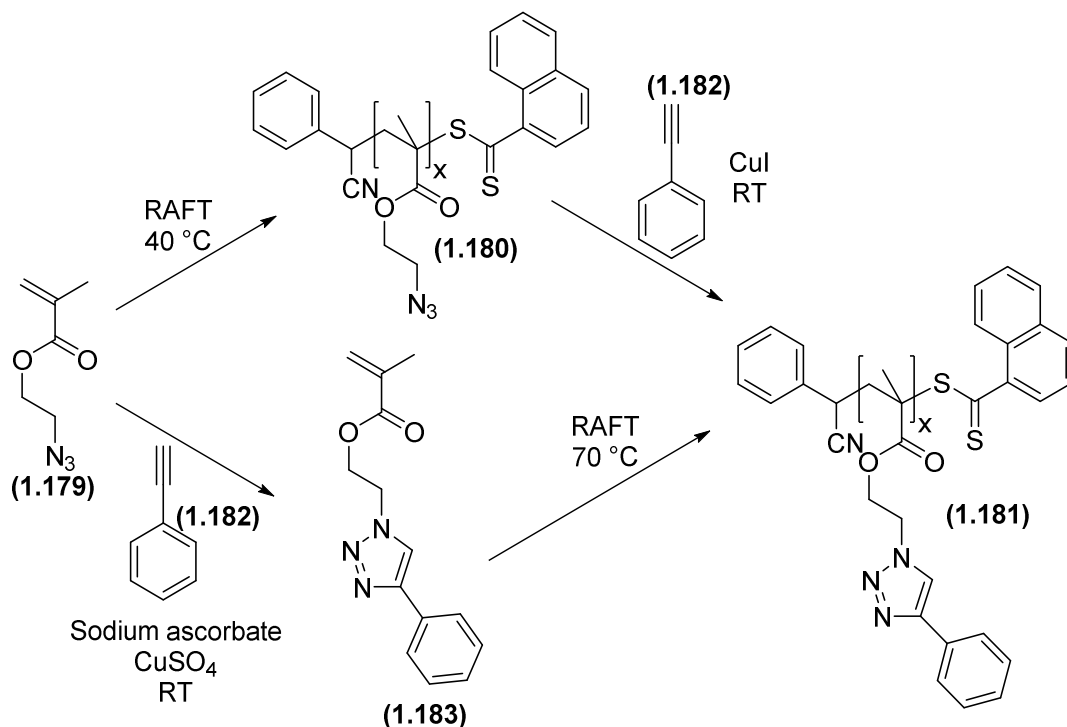
A similar process has been employed by Marref *et al.* to develop self-healing polymers that would decross-link upon heating and cross-link upon cooling (**Scheme 1.36**).^[89] Furan–maleimide **1.175** were grafted onto copolymers of polyethylene **1.176**. Heating of material **1.177** allowed for the Diels-Alder reaction to take place and create a cross linked structure **1.178**. This material can be used as a thermally reworkable film.^[88]



Scheme 1.36 - Thermoresponsive Diels Alder – picture from Hall *et al.*^[88]

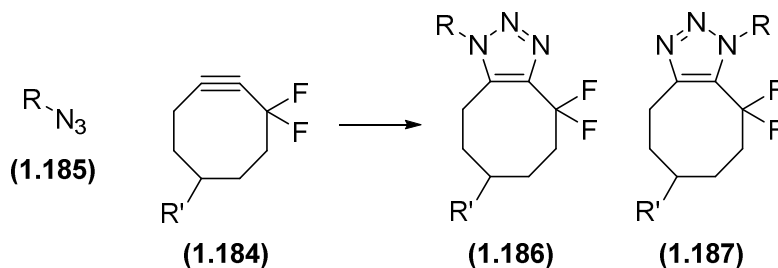
1.5.2 Azide-Alkyne reaction on polymers

Copper-catalysed azide alkyne cycloaddition (CuAAC) is used extensively in polymer functionalisation as well as macromolecule synthesis, as it can often be done in both organic and aqueous media, and is compatible with a wide range of functional groups.^[1] Additionally, both the azide and alkyne functionalities are innocuous to a variety of polymerisation techniques, often preventing the need for deprotection prior to post-polymerisation modification. This was nicely exemplified by Benicewicz *et al.* with their work on the synthesis of a “clickable” polymer **1.180** by the RAFT of 2-azidoethyl methacrylate **1.179** (**Scheme 1.37**). Subsequent CuAAC with phenyl acetylene **1.182** was achieved in full conversion.^[92] Additionally, in a pre-functionalised approach, methacrylate **1.179** was coupled to phenyl acetylene **1.182** to yield monomer **1.183**, which was also subjected to RAFT. The post polymerisation functionalised polymer **1.181** possessed identical ¹H-NMR to that of the pre-functionalised approach, indicating that the azide side chains of **1.180** remain intact during the RAFT polymerisation. Unfortunately, even though azides should not have interfered with the RAFT polymerisation, their thermal instability did require that the polymerisation take place below 50 °C. It was speculated that at elevated temperatures the azide was undergoing decomposition into a nitrene, which was then reacting with AzMA monomers **1.179** via cycloaddition, allowing for the cross linking of polymer strands. This was reflected in an increase in dispersity.



Scheme 1.37 - CuACC functionalisation of poly(AzMA) with phenyl acetylene by Benicewicz *et al.*^[92]

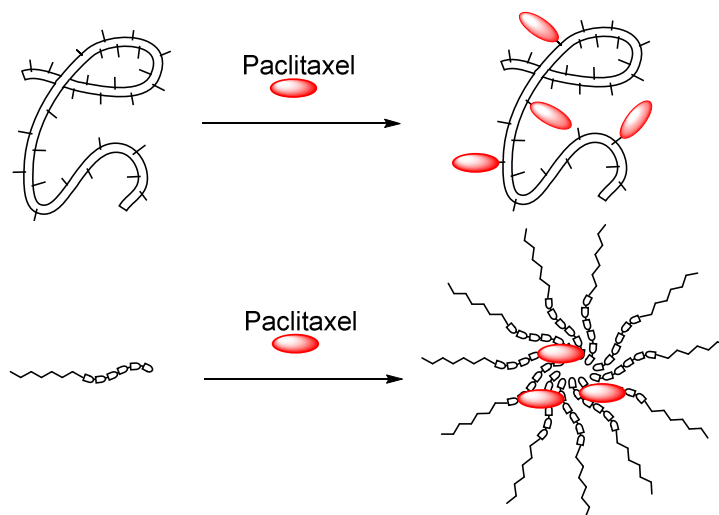
One of the drawbacks to CuAAC is the troublesome removal of residual copper from the product, which complexes with the triazole ring. This can cause problems with solubility as well as biological applications which are sensitive to Cu(I).^[1,93] In the previous example, Benicewicz *et al.* had managed to reduce the Cu(I) content down to 32 ppm after purification,^[92] however this is above the limit for many pharmaceutical applications of 15 ppm.^[94] For this reason, this click process can be achieved using copper free strain-promoted azide alkyne cycloaddition (SPAAC). This was demonstrated by Zou *et al.* when tagging biotin-conjugated cyclooctyne derivatives to azide-substituted substrate bound to a peptidyl carrier protein (PCP).^[95] As in many SPAAC reactions, the cyclooctyne moieties **1.185** used in this case was difluorinated. Introduction of these electron withdrawing groups are used to decrease the energy of the lowest unoccupied molecular orbital (LUMO) of the alkyne, allowing for the cycloaddition to proceed under mild conditions, which is necessary to prevent decomposition of azide **1.185**. (Scheme 1.38).^[96]



Scheme 1.38 - Use of difluorinated cyclooctyne (DIFO) derivatives in a SPAAC reaction.^[96]

1.6 Drug Polymer – Conjugates

As discussed previously, the conjugation of a drug to a polymer can improve the pharmacokinetics of a compound. A notable example of this is the anticancer drug, paclitaxel (marketed as Taxol®), which experiences poor water solubility. For this reason paclitaxel is commonly administered in a surfactant formulation of Cremophor EL (CrEL); a polyoxyethylated castor oil with anhydrous ethanol, which results in severe side effects in patients such as hypersensitivity reactions and neurotoxicity.^[97,98] Strategies to avoid the use of CrEL and improve drug delivery have been investigated, which include polymer-drug conjugates and polymer-drug micelles (**Scheme 1.39**).

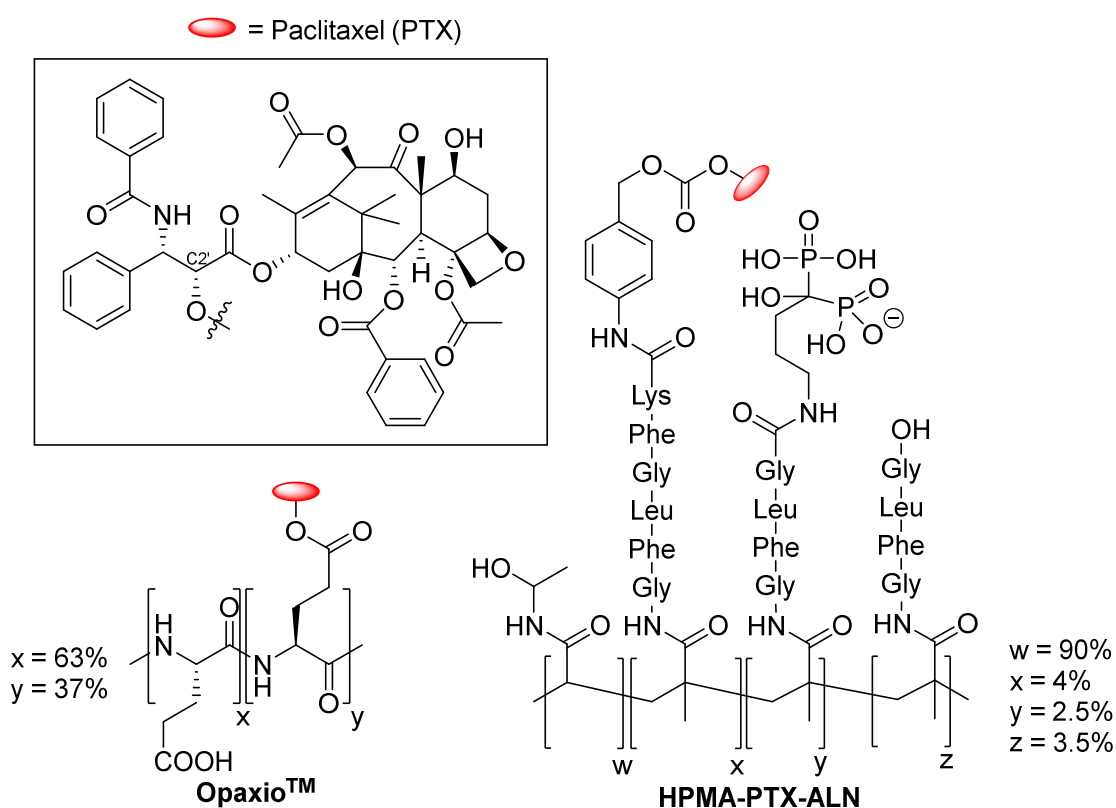


Scheme 1.39 - Schematic representation of polymer-paclitaxel conjugates (I) and polymeric-paclitaxel micelles (II).^[99]

Polymer-paclitaxel conjugates include Opaxio™, a poly(glutamic acid)-paclitaxel PGA-PTX conjugate currently in phase III clinical trials for the treatment of brain cancer (**Scheme 1.40**). Opaxio™ offers greater water solubility and antitumor activity as compared to free PTX.^[97] However, conjugation of the hydroxyl at the C2' position of paclitaxel with pendent

carboxylic acids of PGA proceeds without control over the placement of the drug along the polymer backbone, resulting in poorly defined polymer aggregates.^[100] This statistic distribution along the polymer chain results in moderate loading of paclitaxel (37 wt%), as loading above this value resulted in poor dispersion of the conjugate in solution.^[99,100]

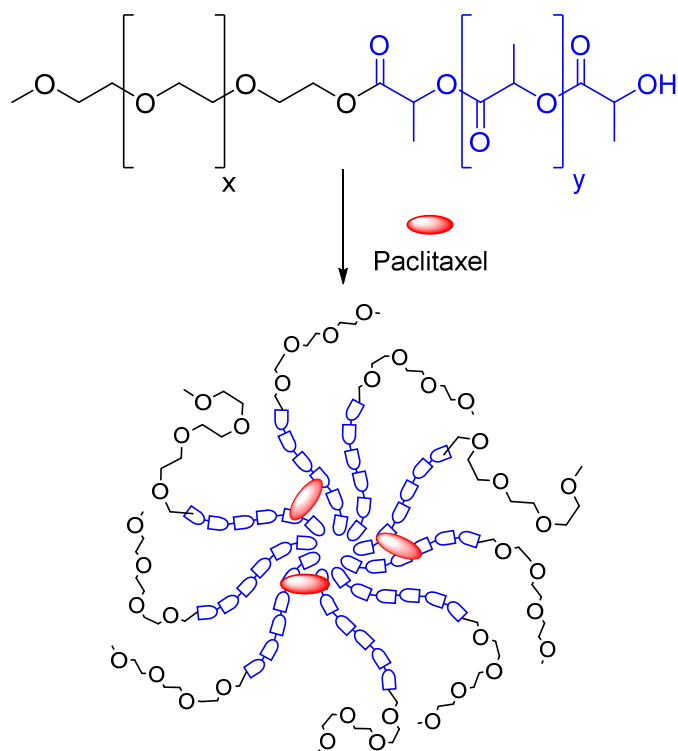
Studies have also been investigated using poly(hydroxypropylmethacrylamide) (HPMA) coupled to both PTX and the bone targeting agent alendronate (ALN) (HPMA-PTX-ALN) (**Scheme 1.40**).^[101] This polymer-drug conjugate offers improved delivery of PTX to the bones due to the targeting action of ALN. Both ALN and PTX are conjugated to HPMA via peptide linkers that are cleaved by Cathepsin B, a lysosomal enzyme that is overexpressed in tumour endothelial and epithelial cells.^[102] Unfortunately, loading of PTX is relatively low. (approximately 5 wt%).^[99,101]



Scheme 1.40 – Paclitaxel-polymer conjugates; Opaxio™ and HPMA-PTX-ALN.

Polymeric micelles (PM) have been proven to be effective drug delivery agents due to their size in the nanorange, which can exploit the enhanced permeability and retention effect (EPR), as well as offering high stability in plasma and longevity *in vivo*.^[103] Genexol-PM®; a PEG and poly(D,L-lactic acid) (PDLLA) copolymer-based PM has shown to be an effective way to delivery PTX (**Scheme 1.41**).^[26] Genexol-PM demonstrated a 3-fold increase in the maximum dose tolerance (MTD) due to its decrease in side effects compared to free PTX. It also showed a significantly increase anti-tumour efficacy. Genexol-PM has been approved by the FDA for the treatment of patients with breast cancer.^[26] Other notable examples are

paclitaxel-based Abraxane[®], an albumin-bound conjugate and EndoTAG[®], a liposome based system.^[97]



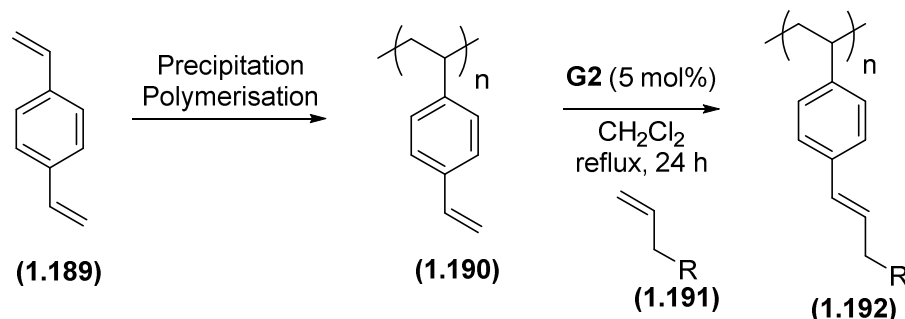
Scheme 1.41 – Schematic representation of micelle; Genexol-PM[®].^[99]

Cell recognition by drugs/polymers can be achieved by interaction with integrins, which are transmembrane receptors that act as bridges between cell-cell and for cell-extracellular matrix.^[104] When triggered, integrins can generate a biochemical cascade responsible for a range of behaviours such as cell adhesion, cell signalling, apoptosis, tumour angiogenesis and metastasis. Integrins are composed of an α - and β -subunit, of which there are 18 possible α -subunits and 8 possible β -subunits. The combination of these pairs influence the integrin's ligand binding specificity and signalling properties. Most integrins recognise their respective integrin by an exposed tripeptide sequence (arginine-glycine-aspartate, RGD).^[104] This allows drugs that possess this RGD sequence to act as complementary ligands to integrins, such as $\alpha_v\beta_3$, which has been shown selectively expressed on endothelial cells that are undergoing tumour angiogenesis.^[105]

1.7 Previous Work in the Prunet Group

Work by Amaia Altuna focused on the functionalisation of synthetic macromolecules by olefin metathesis.^[106] This project first involved the synthesis of poly(divinylbenzene) **1.190** by precipitation polymerisation to yield insoluble porous beads. CM of residual pendent vinyl groups allowed for the functionalisation of these polymer beads. This functionalisation could

perhaps allow the polymer beads to take part in ion exchange, and overall be used for example as a purification system for drinking water. It was shown that it was possible to perform cross metathesis of poly(divinylbenzene) **1.190** with various coupling partners using **G2**. These coupling partners include methyl acrylate, homoallylamine, allyl glycine and allyl bromide (**Scheme 1.42**).



Scheme 1.42 - Synthesis of insoluble poly(divinylbenzene), and subsequent functionalisation using CM.

Work in the Prunet group has also investigated the cross metathesis between PCA-co-PAGE and methyl acrylate, which has previously been discussed in Section 1.5.1.^[64]

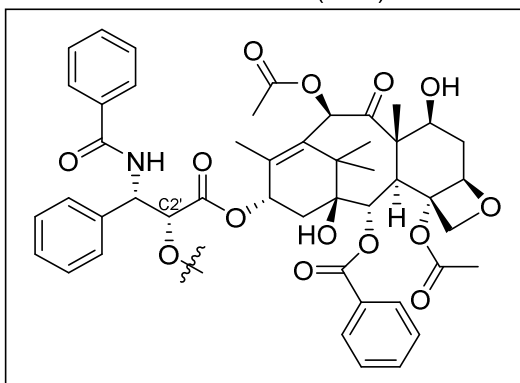
1.8 Project Aim

PEG species are used extensively in biomedical applications, with common functionalising methods including thiol-ene, Diels-Alder, azide alkyne, amongst others, however the use of olefin cross metathesis to functionalise PEG is an unexplored area. To date, the studies of the CM on polymers have focused on polyoxazolines, polyesters and polyolefins, and so expanding this scope to PEG based material may allow for the development of new biocompatible polymers. Additionally, olefin metathesis has the added benefit of retaining the alkene moiety, which would allow for further functionalisation to be carried out, such as fine tuning the hydrophilicity by dihydroxylation.

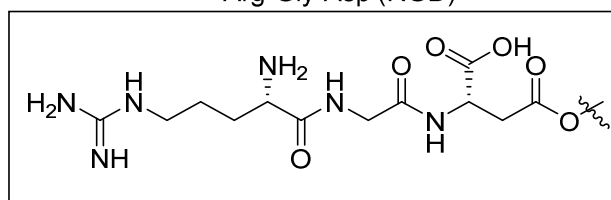
The main aims are as follows:

1. Investigate the CM on PEO-PAGE with discrete molecules such methyl acrylate, and optimise the reaction conditions to achieve maximal conversion and minimal self metathesis.
2. Synthesise new copolymers that allow for the production of a dual functionalised biocompatible polymers, which possesses both a warhead such as PTX and a targeting species such as RGD (**Scheme 1.43**).
3. Couple bioactive compounds PTX and RGD onto the polymer backbone using CM to yield a dual functionalised polymer with retention of monodispersity.

Paclitaxel (PTX)



Arg-Gly-Asp (RGD)



Scheme 1.43 – PTX and RGD

Chapter 2 : Cross Metathesis with small molecules

2.1 Synthesis of PAGE

Initial work investigating the CM on polyethers was conducted using the copolymer poly(ethylene oxide)-*co*-(allyl glycidyl ether), PEO-*co*-PAGE, shown in Figure 2.1, which was supplied to us by the Hawker group.^[37] This polymer was synthesised by copolymerisation of ethylene oxide with allyl glycidyl ether using benzyl alkoxide initiator, yielding a polyether with molecular weight of 25,000 g.mol⁻¹.

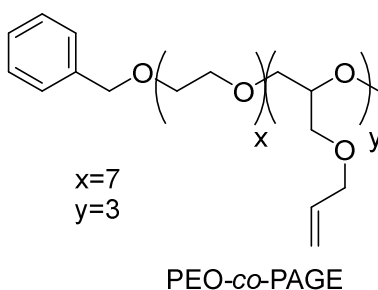
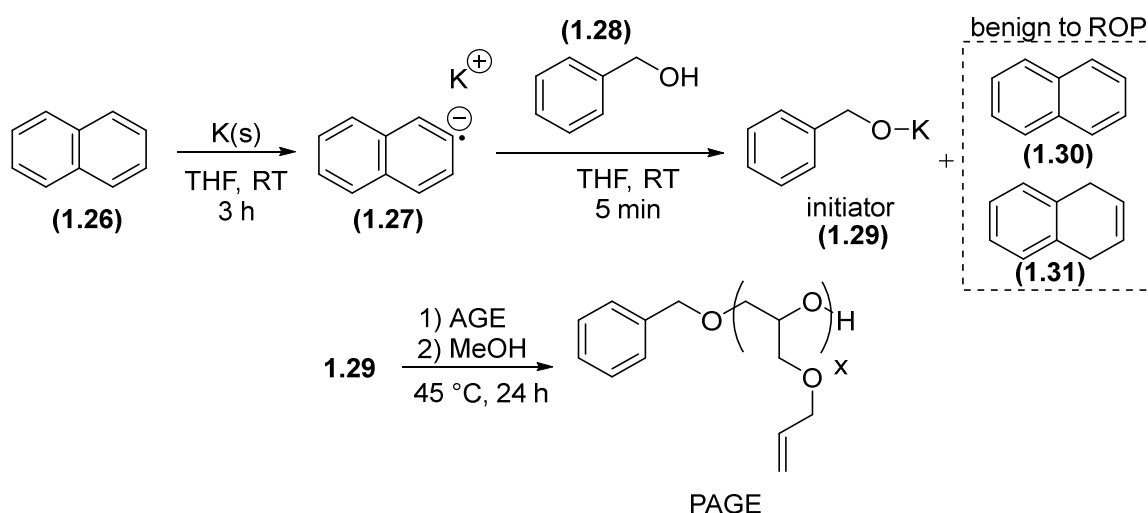


Figure 2.1 - PEO-*co*-PAGE synthesised by the Hawker group.

Initial experiments found that the bulk of the supplied PEO-*co*-PAGE material did not fully dissolve in CH₂Cl₂ or other solvents including methanol, chloroform, THF or toluene. This is in contrast to the polymer described by Hawker *et al.*, however it is believed that the PEO-*co*-PAGE had undergone a similar gelation process described by Erberich *et al.*^[33] For this reason we decided to freshly synthesise PAGE ourselves using the methodology developed by Hawker *et al.* for anionic ROP.^[37]

Synthesis of the initiator starts by the reduction of naphthalene **1.26** using potassium in THF to yield a green solution of potassium naphthalenide **1.27** (Scheme 2.1). This was followed by titration with benzyl alcohol **1.28** to yield colourless benzyloxide initiator **1.29** as well as by products naphthalene **1.30** and dihydronaphthalene **1.31**, which are innocuous to the ROP reaction. Addition of allyl glycidyl ether monomer **1.6** to initiator **1.29** allowed for the ROP to occur with a target M_n of 10,000 g.mol⁻¹. This is a very air/moisture sensitive process and so maintenance of an inert atmosphere was vital, however without a glove box this was exceptionally difficult.



Scheme 2.1 – Polymerisation of allyl glycidyl ether using potassium benzoyloxide.

Polymerisation of AGE monomer **1.6** with initiator **1.29** in THF was initially achieved with little success, with recovery of only starting material (Table 2.1). In an attempt to promote the initiation of the polymerisation, the concentration of **1.29** was increased (entry 2 and 3) as well as increasing the ratio of initiator **1.29** to monomer **1.6** (entry 4), however no polymerisation was observed in each case. We believe that this was perhaps due to THF solvent diluting the monomer, thereby limiting the initiation of the ROP of **1.6**, however it may also be possible that small amounts of moisture in the THF was terminating the ROP reaction.

Entry	[Initiator] mol.L ⁻¹	Initiator : monomer	DP ^a	Observed M _n (g.mol ⁻¹) ^b	Theoretical M _n (g.mol ⁻¹) ^c	Yield ^d (%)
1	0.1	1:88	0	-	10,044	0
2	0.4	1:88	0	-	10,044	0
3	0.7	1:88	0	-	10,044	0
4	0.7	1:44	0	-	5,022	0

Table 2.1 - Attempted polymerisation of allyl glycidyl ether with potassium benzyloxide in THF. ^a DP = degree of polymerisation, ^b Measured by ¹H-NMR, ^c defined by initiator to monomer ratio, ^d b.r.s.m.

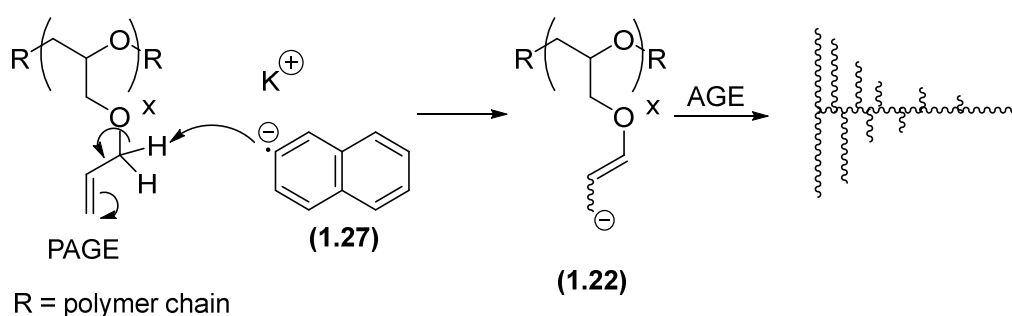
Removal of THF solvent prior to the addition of the monomer allowed for the polymerisation of AGE to proceed, however the observed M_n was significantly lower than the theoretical M_n (Table 2.2). This is potentially due to protic impurities i.e. a slight excess of benzyl alcohol **1.28** that was added during the titration with naphthalenide **1.27**, resulting in

protonation of the propagating chain (chain termination). We attempted to prevent this by using a slight excess of naphthalenide **1.27** prior to addition of monomer **1.6**, however this resulted in gelation of the polymer. This is possibly due to deprotonation at the allylic position of either the unreacted monomers, or the polymer chain to yield carbanion **1.22**. This carbanion could then act as a site for propagation, resulting in a branched or network structure (Scheme 2.2). Additionally, other research groups had reported the isomerisation of the ally group to the 1-propenyl isomer that occurred at elevated temperature.^[32,36,37] In order to prevent this isomerisation, polymerisations were carried out at 30 °C, allowing for suppression of isomerisation.

Entry	Initiator : monomer	DP	Observed M_n (g.mol ⁻¹) ^a	Theoretical M_n (g.mol ⁻¹) ^b	\bar{D}	Yield ^c (%)
1	1:20	27	3,082	2,283	1.13	45
2	1:40	28	3,196	4,566	1.10	44
3	1:50	22	2,512	5,707	1.06	95
4	1:100	72	7,990	11,414	1.08	22

Table 2.2 - Polymerisation of allyl glycidyl ether with potassium benzyloxide neat.

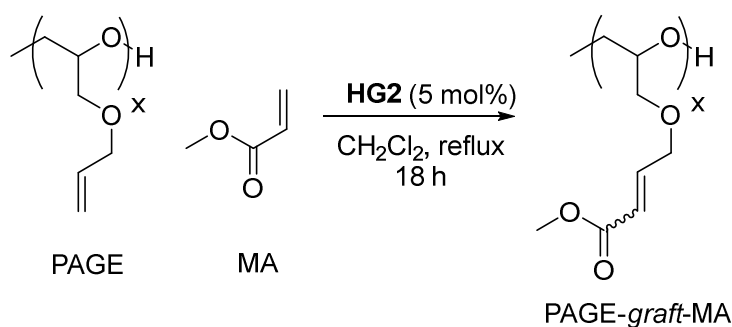
^a Measured by ¹H-NMR, ^b defined by initiator to monomer ratio, ^c b.r.s.m.



Scheme 2.2 – Mechanism of gelation by use of excess potassium naphthalenide.

2.2 Purification of CM polymer product

Although the M_n of the obtained polymers were below the target of 10,000 g.mol⁻¹, we decided to move on to investigating the coupling with methyl acrylate (MA) by CM, as the M_n of the polymer should not influence the reactivity of the pendent olefin handles (Scheme 2.3).



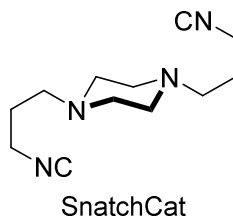
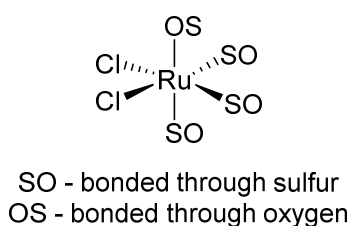
Scheme 2.3 - CM of PAGE with MA

Unfortunately the purification of the conjugated product PAGE-*graft*-MA proved difficult and initially prevented us from carrying out ^1H -NMR analysis. Purification relied on the precipitation of the polymer in hexane. After precipitation it was observed that the polymer would not re-dissolve in CH_2Cl_2 (Figure 2.2), indicating a change in structure during the precipitation process. It is believed that upon precipitation, the polymer and **HG2** catalyst are brought into immediate proximity of each other allowing for intermolecular cross linking to occur via CM, resulting in a network structure that is insoluble in CH_2Cl_2 . It was found that the addition of DMSO to the crude mixture prior to precipitation in hexane could limit this process. Coordination of the DMSO to the ruthenium centre of **HG2** occurs through either the oxygen or sulfur,^[107] thereby displacing the *N*-heterocyclic carbene (NHC) and removing the catalytic activity to CM (Scheme 2.4).

This use of DMSO worked well for short term storage of the polymer (*i.e.* to carry out an NMR analysis), however storing the precipitated polymer for longer than 24 hours resulted in the formation of an insoluble cross linked gel. This highlighted that impact that self-metathesis could have on the polymer. For this reason, we investigated the use of a stronger quenching agent.

The use of the isocyanide species, SnatchCat (Scheme 2.4) proved effective at disabling the self-metathesis process upon storage for prolonged periods of time (measured up to 4 weeks). In order to completely remove the possibility for SM, the PAGE-*graft*-MA was hydrogenated, however this removes the functionality of the polymer, removing the possibility to use the olefin to fine-tune the hydrophilicity by dihydroxylation.

After successful suppression of the cross linking during purification, we then moved onto examining the reaction conditions necessary to attain maximum amount of grafting of MA.



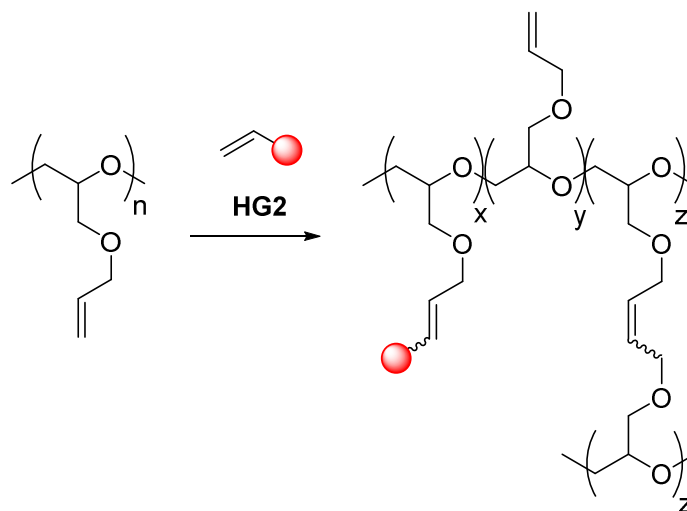
Scheme 2.4 - Methods for quenching ruthenium catalyst.^[107]

Figure 2.2 - Cross linked PAGE-graft-MA.

2.3 Possible products of CM using PAGE

We propose that, in any polymer subjected to a CM reaction, there are three potential outcomes for each pendent olefin; successful coupling, no reaction, and self-metathesis (Scheme 2.5). By comparing the ¹H-NMR integration of each olefin signal it is possible to determine the ratios of x:y:z.

Unfortunately, the production of three different products on the same polymer chain, each with a different molar masses, complicates the calculation of the yield, since the average molar mass of a repeating unit (\bar{M}_p) will depend on the ratios of x:y:z. For this reason, the theoretical yield is calculated *after* ¹H-NMR of the product has been used to calculate \bar{M}_p using Equation 5.



Scheme 2.5 - Potential outcomes of olefin handle (x = conversion into desired product, y = unreacted olefin, z = self metathesis)

$$\bar{M}_p = \left[\left(\frac{M_x \times a}{100} \right) + \left(\frac{M_y \times b}{100} \right) + \left(\frac{M_z \times c}{100} \right) \right]$$

Equation 5

\bar{M}_p = molar mass of polymer

M_x = molar mass of region x, a = percentage of species x,

M_y = molar mass of region y, b = percentage of species y,

M_z = molar mass of region z, c = percentage of species z.

An example of these three distinct products can be seen in the ^1H -NMR spectrum of PAGE-graft-MA, which clearly shows the electron deficient protons (X1 and X2) of the grafted MA region, as well as the two terminal olefinic protons (Y2 and Y3) (Figure 2.3). The occurrence of self-metathesis can also be seen at 5.78 ppm. We have ascertained that this signal is due to SM as it is identical to the one seen when PAGE was subject to CM in the absence of a coupling partner.

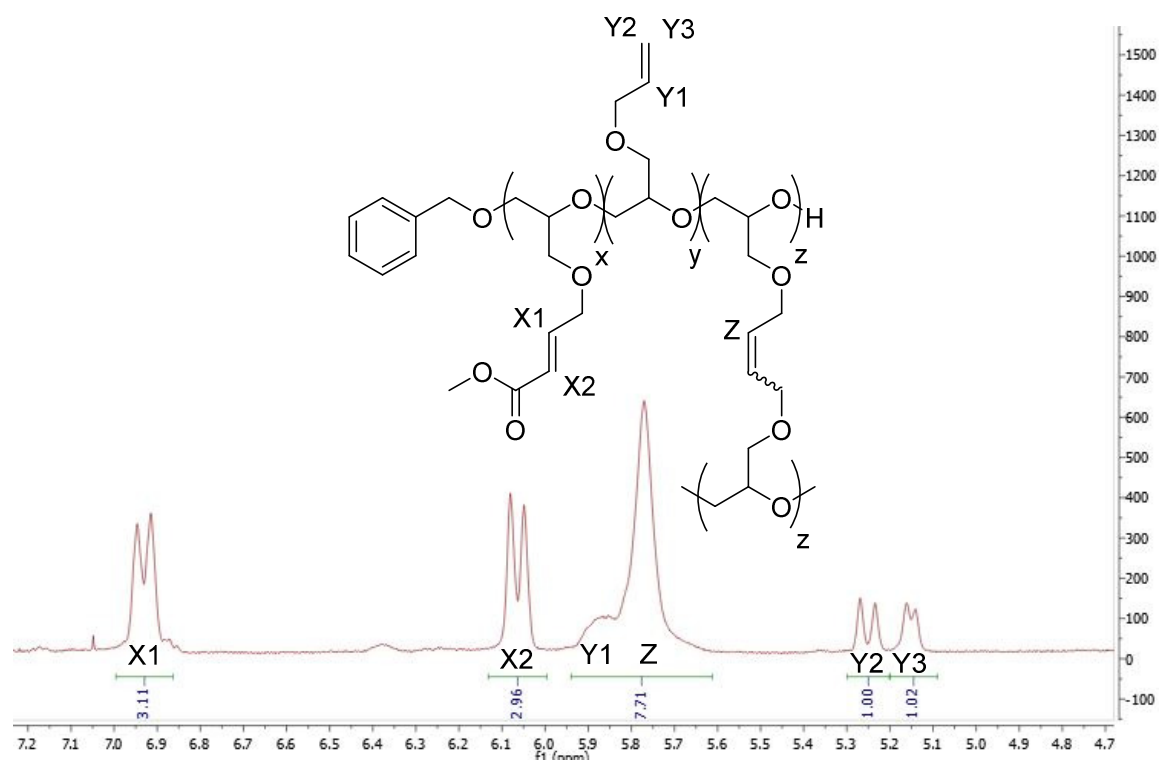


Figure 2.3 - PAGE-graft-MA.

The degree of successful coupling (conversion) is inversely proportional to the degree of SM. The reversibility of the olefin metathesis reaction means that the SM olefin should eventually equilibrate towards PAGE-*graft*-MA *i.e.* the thermodynamic product, however this is not the case as we observe SM even when the reaction has been left for prolonged periods of time. This may be due to conformation of the polymer, which could prevent either the **HG2** catalyst or MA from accessing the site of self-metathesis and allowing for sequential coupling with MA. This theory is also supported by the presence of unreacted terminal olefins as seen in **Figure 2.3**. These alkenes are type 1 in nature and should rapidly homodimerise, however their presence in PAGE-*graft*-MA indicate that they are shielded from the reaction media. It should be noted however that when the levels of SM are high, the observed NMR spectrum is broad, resulting in a greater degree of error when calculating the ratios of $x:y:z$. Additionally, this broadening prevents us from distinguishing between *E* and *Z* olefins.

After developing our understanding of how to analyse these polymers, we then moved onto optimising the CM reaction conditions.

2.4 Optimisation of CM reaction with MA.

Previous work in the group by Alice Gonzalez had indicated **HG2** to be an optimal catalyst for CM with polyesters, however we wanted to confirm this was true for PAGE.^[64] **G1** is more commonly used for RCM, and so it was not surprising that this catalyst gave a low conversion ($x = 65\%$). Use of the **G2** catalyst (a more common catalyst for CM) afforded a good conversion of 81%. Most notably, the use of the more stable **HG2** catalyst allowed for the highest conversion of 90% (**Table 2.3**).

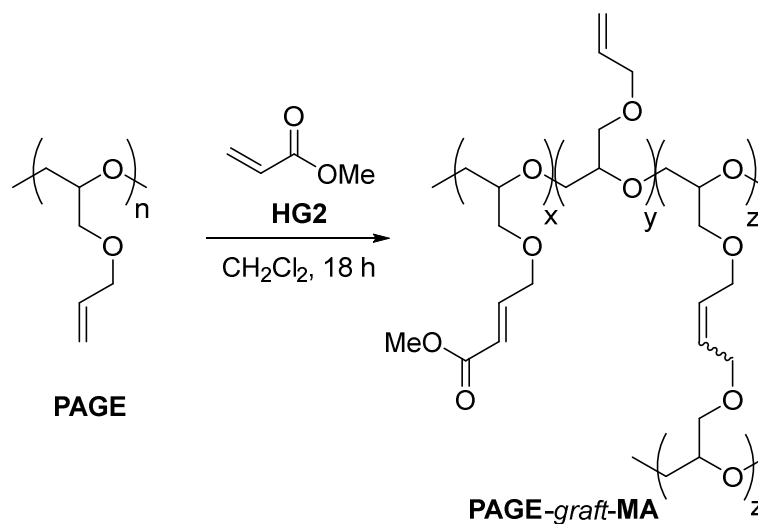
Catalyst	Conversion (%)
G1	65
G2	81
HG2	90

Table 2.3 – Various catalyst effect on conversion of PAGE with methyl acrylate (4 eq.) reflux in CH₂Cl₂ for 18 h at a concentration of 0.2 M relative to PAGE.

Previous work by Alice Gonzalez with methyl acrylate (MA) had shown that reflux of 4 equivalents of MA at a 0.2 M concentration of polymer had resulted in successful CM with PAGE, however there was still evidence of self metathesis (Scheme 2.6) (Table 2.4, entry 1). Various conditions were examined in an attempt to limit SM, however it was first important to confirm that homodimerisation of the pendent alkenes was indeed the cause of this signal at 5.78 ppm. We had already confirmed that this signal was the predominant product when PAGE was reacted with **HG2** in the absence of MA, however it was also possible that isomerisation of the terminal olefin to the enol ether was the cause for this apparent change in structure.^[108] If this was to be true, the most likely source would be a ruthenium-hydride species such as **1.72**, which would be produced by the decomposition of **HG2**. Work by Grubbs *et al.* has shown *p*-benzoquinone to be effective in preventing this isomerisation by acting as a hydride scavenger. However use of *p*-benzoquinone additive resulted in a decreased conversion of polymer (Table 1, entry 2 and 3). Lowering the temperature may have lowered the rate of homodimerisation of PAGE, however this also reduced the ability of the polymer to conjugate with MA resulting in a decrease in conversion (entry 4).

Changes in concentration resulted in the most effective change in conversion. Decreasing the concentration from 0.2 M to 0.1 M (entry 5) resulted in a decrease in conversion from 75% to 60%, which was expected as the decrease in concentration reduces the likelihood of the PAGE coupling with the MA. Even when the number of equivalents of MA was doubled at this lower concentration, there was little change in conversion of the polymer

(entry 6). Reaction of PAGE in MA as a solvent offered a moderate conversion of 78% (entry 7). This indicates that, at a concentration of 0.1 M, the number of equivalents of MA is not the limiting factor in preventing SM of PAGE.



Scheme 2.6 – CM of PAGE with MA using **HG2** catalyst

Entry	Equivalents of MA	Molarity w.r.t PAGE	Temperature (°C)	Additive	x:y:z ^a	Yield ^b (%)
1	4	0.2	45	-	75:1:24	73
2	4	0.2	45	<i>p</i> -Benzoquinone (0.2 eq)	47:7:46	93
3	4	0.2	45	<i>p</i> -Benzoquinone (0.4 eq)	54:2:44	93
4	4	0.2	0	-	30:9:61	85
5	4	0.1	45	-	60:2:38	80
6	8	0.1	45	-	63:0:37	85
7	neat	0.2	45	-	78:0:23	87
8	4	0.4	45	-	98:0:2	95
9	8	0.4	45	-	95:0:5	92
10 ^c	4	0.4	45	-	85:0:15	91

Table 2.4 - CM of PAGE with MA using **HG2** (5 mol%). ^a x = PAGE-graft-MA, y = unreacted PAGE, z = self metathesis. ^b calculated using adjusted molar mass (Equation 5). ^c Slowly added 0.4 M of PAGE in CH₂Cl₂ to reaction mixture of MA and **HG2** in CH₂Cl₂.

The best results came when the concentration was increased to 0.4 M as this led to 98% conversion (entry 8). Theoretically, an increase in concentration should result in an increase in intermolecular SM, however the apparently decrease in SM could be due to two factors. Firstly, homodimerisation may be occurring preferentially in an intramolecular fashion. This should lead to a folded conformation, such as the ones reported by Coates *et al.* while investigating the CM of polycarbonates.^[68] Production of a folded conformation would also explain the presence of unreacted terminal alkenes that are seen in many polymers where SM is prevalent, as these unreacted pendent alkenes could be internalised within the macromolecule, and therefore hidden from the reaction media. When high levels of self metathesis are observed, the ¹H-NMR olefin signal corresponding to the homodimerised alkene is very broad and thus little information can be gained about the chemical structure of the alkene; however the low degree of SM seen in entry 8 resulted in clear resolution of the signal at 5.78 ppm in the ¹H-NMR spectrum (Figure 2.4). *J*-coupling of 11.4 Hz indicated the presence of *cis* olefin, which corresponds to a relatively low strained 12-membered ring resulting from the RCM between two adjacent pendent alkenes (Scheme 2.7). If this SM was intermolecular, it would likely yield the thermodynamic *trans* olefin that would have a *J*-value closer to 17.0 Hz.

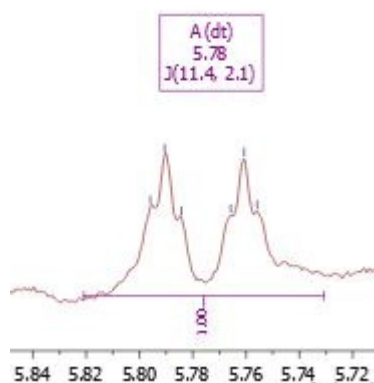
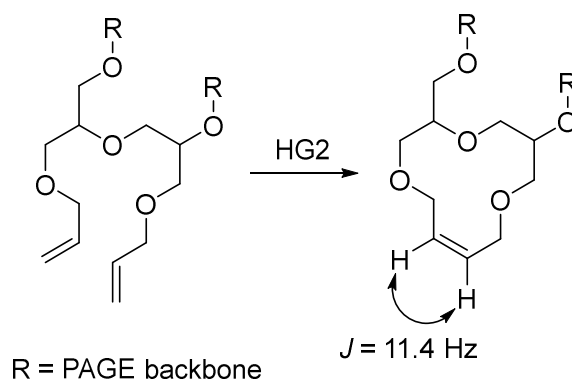


Figure 2.4 - NMR doublet of triplets from intramolecular SM.

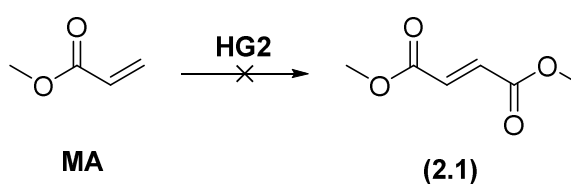


Scheme 2.7 – Intramolecular SM to yield 12-membered cycloalkene.

Secondly, an increase in concentration should facilitate the coupling of PAGE with MA in the early stages of the reaction, which could then sterically hinder the SM of the polymer strand. However in light of the result of the reaction of PAGE in a neat solution of MA (entry 7), we propose that the number of equivalents of MA plays a lesser role in preventing SM than the concentration of PAGE does. This was confirmed when the equivalents of MA were

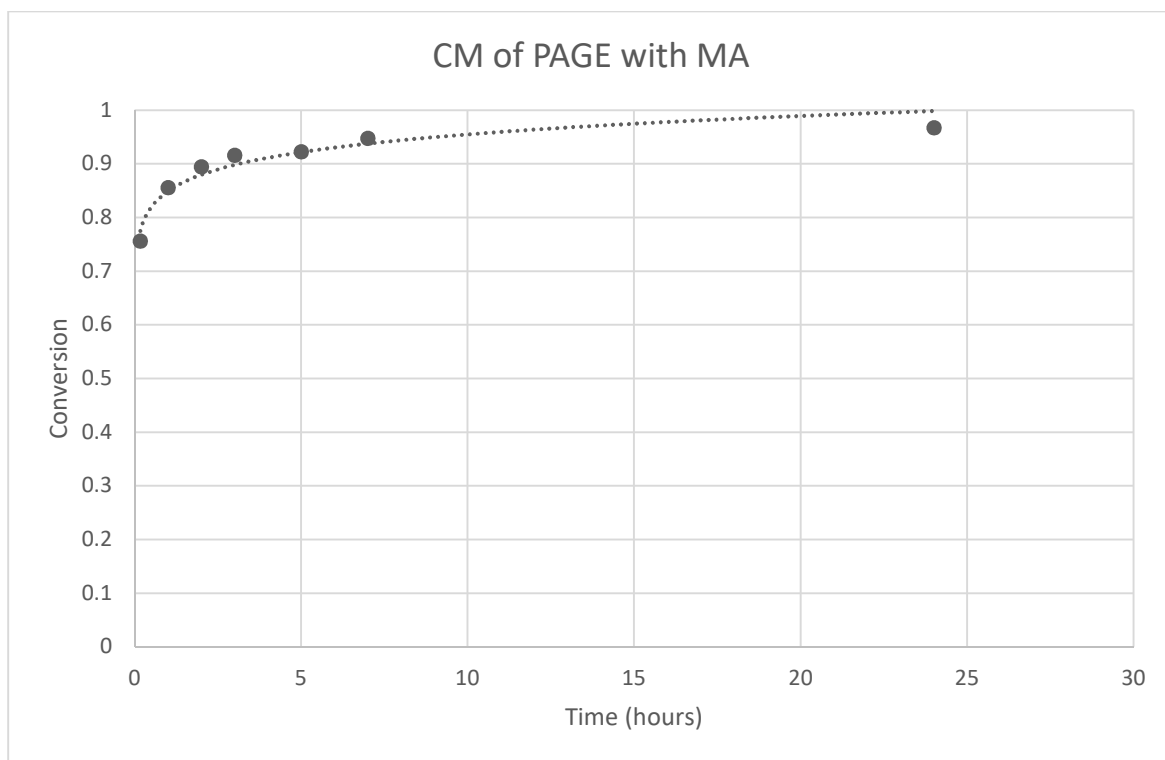
increased whilst maintaining a high concentration (entry 9), which resulted in a slight decrease in concentration, likely due to dilution of the concentration of **HG2**.

Finally we proposed that slow addition of PAGE to a solution of MA and **HG2** may allow to artificially increase the number of equivalence of MA relative to PAGE, whilst preventing dilution of the **HG2** catalyst. NMR analysis of the CM reaction was carried out at 1 hour time intervals in order to gain insight into how fast this successful coupling to the polymer was occurring, and overall it was found that PAGE achieved ~85% conversion within the first hour (Graph 2). As a result of this finding we decided to conduct the slow addition of PAGE to a reaction mixture over 1 hour, as this time should be sufficient to prevent the accumulation of unreacted PAGE (entry 10). Under these conditions we found that the conversion decreased to 85%. This could be further evidence that when the number of equivalents of MA is greatly increased, the CM of PAGE with MA is limited. We also considered that homodimerisation of the abundant MA could be occurring, which would decrease the ability for **HG2** to facilitate the CM of PAGE with MA. However, we do not believe homodimerisation of MA is occurring as we did not recover any dimethyl fumarate upon column chromatography (**Scheme 2.8**).



Scheme 2.8 – Homodimerisation of MA (not observed)

Overall we found that a higher concentration of PAGE yielded the optimal conditions for conjugation with MA. Using these conditions we reacted MA with PAGE of various M_n reported in **Table 2.2**, and we found almost identical ratios of x:y:z across the polymer range. With regards to the structure of the SM product of the polymer we believe that a combination of both intramolecular and intermolecular CM is resulting in the polymer conformation that to a certain degree can shield the pendent allyl handles from subsequent conjugation with MA.



Graph 2 - CM of 0.4 M PAGE with MA (4 equiv) in CDCl_3 at 30 °C.

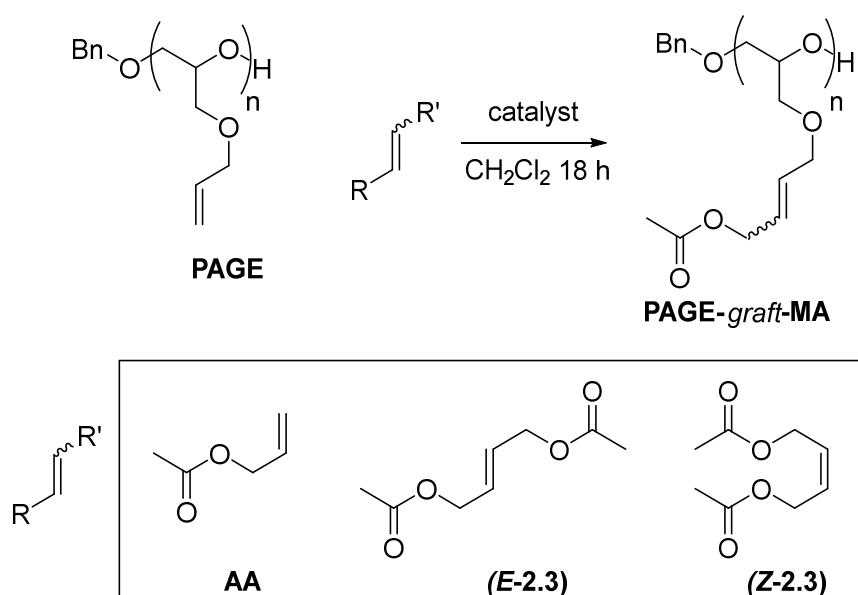
2.5 Optimisation of CM reaction with allyl acetate

While optimising the reaction conditions using MA (type 2 olefin), we also investigated how efficiently a type 1 coupling partner could undergo cross metathesis with PAGE. Type 1 olefins have continued to be difficult coupling partners for CM, due to their tendency to homodimerise and cause a high turn over number (TON) of catalyst, which in turn can lead to undesired side products. In order to study this, allyl acetate was initially chosen as a coupling partner for two reasons; a) it is small in size, and so any low conversion results would most likely not be due to steric hindrance along the polymer backbone, and b) the characteristic CH_3 signal would be easily observed by $^1\text{H-NMR}$.

When this CM reaction was first conducted (Scheme 2.9) a low conversion of 32% was achieved. This was expected due to allyl acetate's ability to homodimerise, exemplified by the recovery of dimer **2.3** as a *E:Z* ratio of 10:1 in a 50% yield. It was proposed that the conversion could be improved by the addition of another four equivalents of allyl acetate after a 12 hour period; however, surprisingly this resulted in a decrease in conversion to 24% (entry 2). This decrease in conversion is potentially due to the increase in the ratio of AA:PAGE, allowing for the active **HG2** catalyst to promote the homodimerisation of AA,

therefore limiting the successful coupling of AA with PAGE. In general, **HG2** is a less reactive catalyst towards CM than **G2** (due to the boomerang effect of the isopropenylstyrene moiety), which may be limiting the coupling of a self-metathesis olefin with AA, resulting in the retention of a self-metathesis product once it has been formed. However, when **HG2** was replaced with **G2**, we observed a slight decrease in conversion from 32% to 28% (entry 3). This is possibly due to the highly reactive **G2** facilitating rapid homodimerisation of AA.

In cases of a type 1 coupling partner, use of the preformed homodimer is commonly used in order to a) prevent the dimerisation of the type 1 species from dominating the catalytic cycle, and b) limit the formation of the less stable ruthenium methyldiene species, which can result in undesirable side products.^[52] Reaction of *trans*-2-butene-1,4-diol diacetate **2.3** with PAGE resulted in an increase in conversion to 60% and 54% when **HG2** and **G2** were used, respectively (entry 4 and 5). Use of *cis*-2-butene-1,4-diol diacetate **2.4** led to an improved conversion of 85%, which is likely due to the alkylidene species of PAGE-Ru preferentially coupling with thermodynamically unstable *Z*-alkene coupling partner as opposed to undergoing self-metathesis (entry 7). Unfortunately, under CM conditions the *Z*-alkene **2.4** isomerises to the *E*-alkene **2.3** over time, which diminishes the observable benefit of the *Z*-alkene coupling partner as the reaction proceeds. Potentially lowering the number of equivalents of *Z*-alkene coupling partner could prevent the **HG2** catalyst from spending the majority of the time facilitating the conversion of the coupling partner from the *Z* isomer to the *E* alkene, and instead allow the catalyst to react with PAGE. Unfortunately, this decrease in equivalence of *Z*-alkene coupling partner led to a decrease in conversion to 65% (entry 8). Decomposition of the catalyst may have been limiting the degree of conversion, and so we investigated using two loadings of **HG2** catalyst separated by a 4 hour interval. This led to an increased conversion of 95% (entry 9).



Scheme 2.9 - CM of PAGE with allyl acetate (1:4 equiv, conc = 0.2 M)

Entry	Coupling partner	Equivalents of AA	Molarity w.r.t PAGE	Catalyst	x:y:z ^a	E:Z selectivity	Yield ^b (%)
1	AA	4	0.2	HG2	32:46:22	6:1	75
2	AA	4 + 4	0.2	HG2	24:49:27	6:1	91
3	AA	4	0.2	G2	28:51:21	6:1	68
4	<i>E</i> -2.3	4	0.2	HG2	60:12:28	7:1	80
5	<i>E</i> -2.3	4	0.2	G2	54:8:38	7:1	64
7	<i>Z</i> -2.3	4	0.2	HG2	85:2:13	8:1	87
8	<i>Z</i> -2.3	2	0.2	HG2	65:7:28	7:1	89
9	<i>Z</i> -2.3	4	0.2	HG2 (2x2.5%)	95:0:5	9:1	72
10	<i>Z</i> -2.3	4	0.4	HG2	90:5:5	9:1	79
11	<i>Z</i>-2.3	4	0.4	HG2 (2x2.5%)	98:0:2	9:1	92
12	<i>Z</i> -2.3	20	neat	HG2	94:3:3	9:1	80

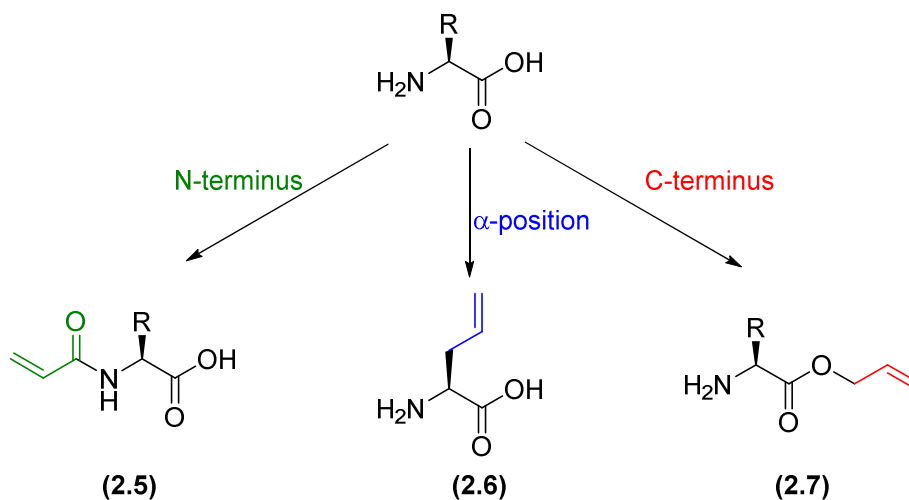
Table 2.5 - CM of PAGE with allyl acetate derivatives. ^a x = PAGE-graft-AA, y = unreacted PAGE, z = self metathesis. ^b calculated using adjusted molar mass (Equation 5).

It was at this time, while studying the CM of PAGE with MA that we discovered the importance of concentration in achieving high conversion. Indeed when we increased the concentration from 0.2 to 0.4 M using *Z*-alkene coupling partner we observed an improvement in conversion from 65% to 90% (entry 8 vs 10). As stated previously, this is likely due to the high concentration allowing for an increased rate of coupling of PAGE with allyl acetate in the early stages of the reaction, leading to retardation of self-metathesis. By using a combination of increased concentration and sequential dosing of **HG2** we observed our highest conversion of 98% (entry 11). We also investigated using *Z*-alkene coupling partner as the solvent, whilst mainlining the concentration relative to PAGE, however we saw a slight decrease in conversion to 94% (entry 12). Overall, we found that use of high concentration in conjunction with multiple loadings of **HG2** catalyst allowed for the highest degree of conversion.

Additionally there was a clear relationship between the degree of conversion and the *E*:*Z* diastereomeric ratio of the conjugated polymer. We believe primarily that an increase in conversion leads to steric crowding around the polymer backbone, resulting in a strong drive for the grafted sites to achieve the most thermodynamically favoured position (*E*-alkene), as this will allow for the least steric interaction of the pendent arms.

2.6 Optimisation of CM reaction with amino acids

Following on from our work with MA and AA, we were eager to investigate the coupling of amino acids and peptides to the polymer, with the ultimate goal of synthesising an RGD conjugated polymer. However firstly we investigated the synthesis of protected amino acids, with an interest in finding the optimal position to install the olefin group in order to achieve high conversion of cross-metathesis reactions. There are three possible positions that have been investigated (Scheme 2.10).

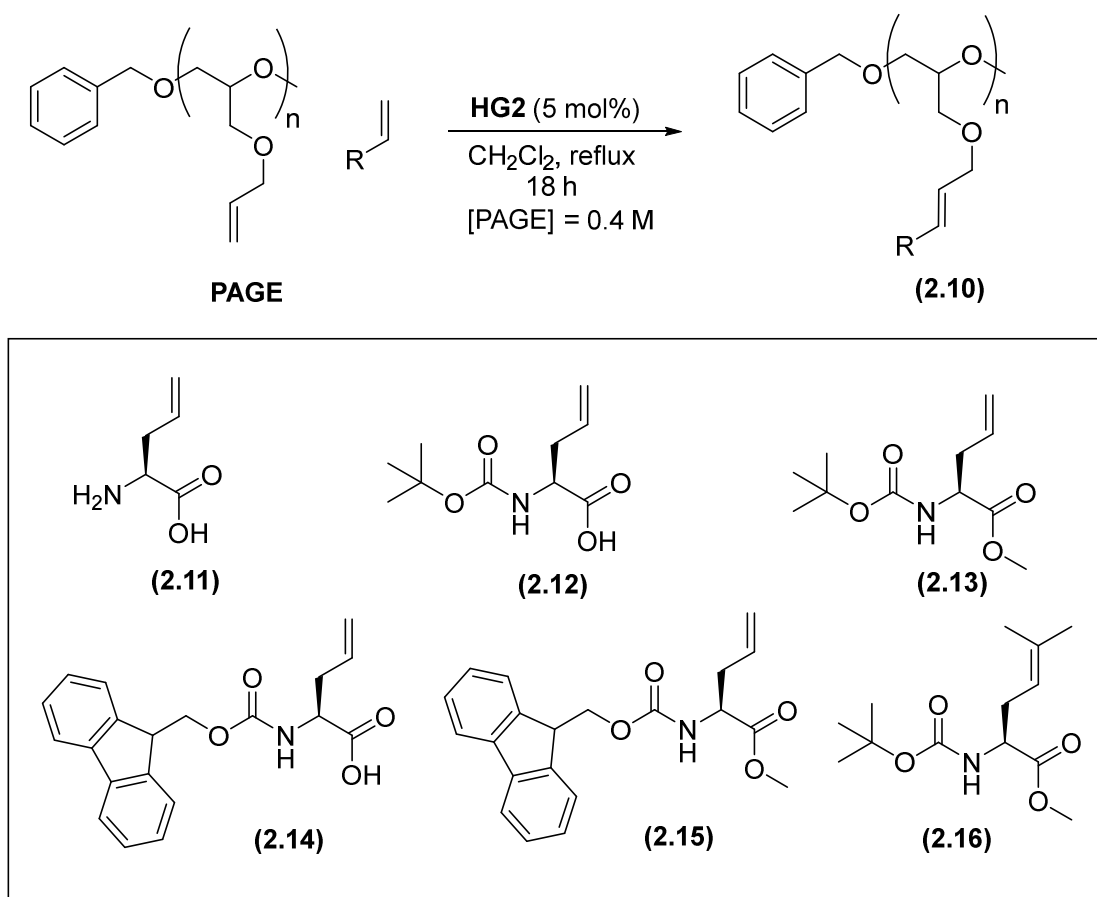


Scheme 2.10 - Positions of olefin on amino acids .

2.6.1 CM with amino acids bearing side chain alkenes

We first investigated various allyl glycine derivatives with an olefin installed at the α -position (Scheme 2.11). Allyl glycine derivatives are interesting coupling partners as they can be integrated into cyclic peptides, and therefore allow the coupling such cyclic structures onto the polymer backbone.

Protection of the amino and carboxylic acid groups of allyl glycine **2.11** was necessary before the cross-metathesis reactions as there is potential for these groups to deactivate the Grubbs catalyst by complexation with the ruthenium centre. This is especially true for the amine group as it possesses a lone pair of electrons that would have a strong affinity for the 14-electron metal complex that is formed during the catalytic cycle.



Scheme 2.11 – CM of PAGE with allyl glycine derivatives

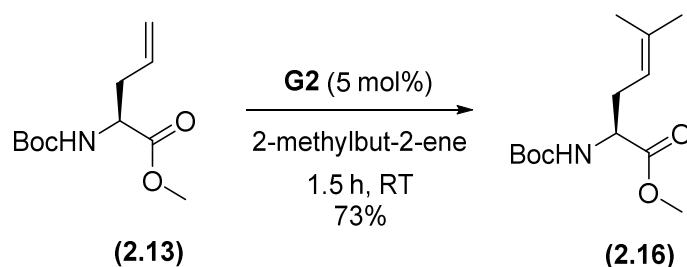
Entry	Coupling partner	x:y:z ^a	Yield ^b (%)
1	2.11	5:90:5	-
2	2.12	30:5:65	-
3	2.13	35:5:60	-
4	2.14	22:7:71	-
5	2.15	26:3:71	-
6	2.16	Cross-linking	-

Table 2.6 - CM of PAGE with allyl glycine derivatives ^a x = PAGE-graft-X, y = unreacted PAGE, z = self metathesis. ^b calculated using adjusted molar mass (Equation 5).

Cross metathesis of unprotected **2.11** with PAGE resulted in the expected low conversion and low degree of self metathesis, due to deactivation of the **HG2** catalyst by the free amine and carboxylic acid groups of **2.11** (Table 2.6, entry 1). Protection of the N-terminus with a Boc group allowed for **2.12** to couple to PAGE with 30% conversion, however a large degree of self metathesis was observed (entry 2). Use of the methyl ester species **2.13** allowed for a slight improvement to 35% conversion, however this was a long way off the desired full conversion (entry 3). Use of Fmoc protected allyl glycines with a free carboxylic acid **2.14** and methyl ester **2.15** yielded 22% and 26% conversion respectively (entry 4 and 5). This decrease in conversion when using Fmoc as opposed to Boc is possibly due to the increase in steric hindrance around the polymer backbone due to the large size of the fluorenyl moiety.

We hypothesised that the rapid homodimerisation of the type 1 of allyl glycine analogues were limiting the successful CM pathway. The use of a preformed dimer had proved successful when investigating the CM of PAGE with allyl acetate, however when we tried to form the homodimer of allyl glycine **2.13** by CM using **HG2** we retrieved a mixture of compounds that were inseparable by column chromatography. This lack of propensity to homodimerise indicates that allyl glycine species may not be favourable to CM conditions, which is a finding expressed in the literature.^[109] However in a final effort we looked at an alternative less reactive trisubstituted allyl glycine **2.16**. This species would be unlikely to undergo homodimerisation, and may therefore allow for a more efficient coupling of the allyl glycine species with PAGE. Alkene **2.16** was synthesised by reacting **2.13** in a neat solution of 2-methylbut-2-ene (Scheme 2.12). Unfortunately, upon reacting **2.16** with PAGE we observed rapid cross linking (entry 6) since the coupling partner was type 3 in nature and unable to readily take part in the CM pathway.

Overall, we did not achieve high conversion of allyl glycine species with PAGE, which is potentially due to ally glycine undergoing unidentifiable side reactions under CM conditions. Note that the yields have not been reported here as the ¹H-NMR of these allyl glycine functionalised polymers were not clean, and contained unexpected signals that we could not assign.

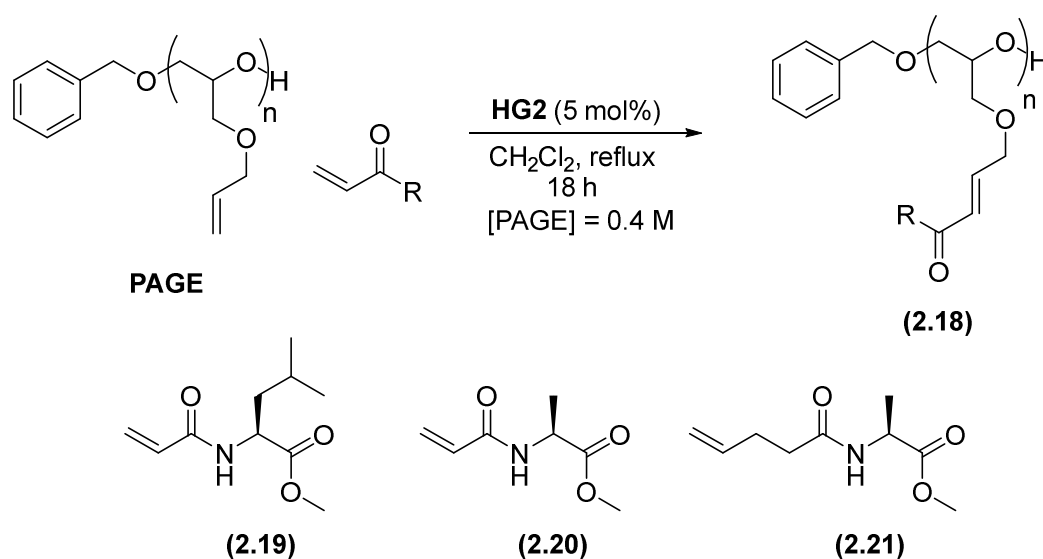


Scheme 2.12 - Conversion of allyl group from type 1 to type 3.

2.6.2 CM using amino acids bearing N-terminus alkenes

Next we moved onto investigating how an alkene installed at the N-terminus of allyl glycine would behave under CM conditions with PAGE. With the results of methyl acrylate in hand it was decided to emulate the alkene reactivity by installing an acrylamide on the N-terminus. Leucine was chosen as an amino acid, as the terminal CH₃ protons gave a characteristic signal that is easily identifiable on the ¹H-NMR spectrum (Scheme 2.13).

CM of acrylamide **2.19** with PAGE allowed for 64% conversion, however we noticed a significant retention of the pendent allyl group of PAGE, indicating that the catalyst was perhaps being deactivated and preventing CM of self metathesis to occur (Table 2.7, entry 1). Use of a slightly less bulky acrylamide coupling partner **2.20** also yielded low conversion (entry 2). We believe that the close proximity of the nitrogen to alkene may be allowing for coordination with the ruthenium centre of **HG2**, thereby disabling it. We postulated that increasing the distance of the nitrogen from the alkene may allow for more efficient CM. Unfortunately upon reacting acrylamide **2.21** we observed a further decrease in conversion to 24%. Homodimerisation of **2.21** was potentially preventing efficient conversion, and therefore we attempted to pre-form the homodimer. Unfortunately upon subjecting **2.21** to CM conditions we observed only trace amounts of the corresponding dimer, firmly indicating that these N-terminus alkenes were not favourable to CM conditions. Overall, we found that an N-terminus functionalised alkene resulted in very poor conversion, which we attribute to the amide functionality interacting unfavourably with the ruthenium catalyst.



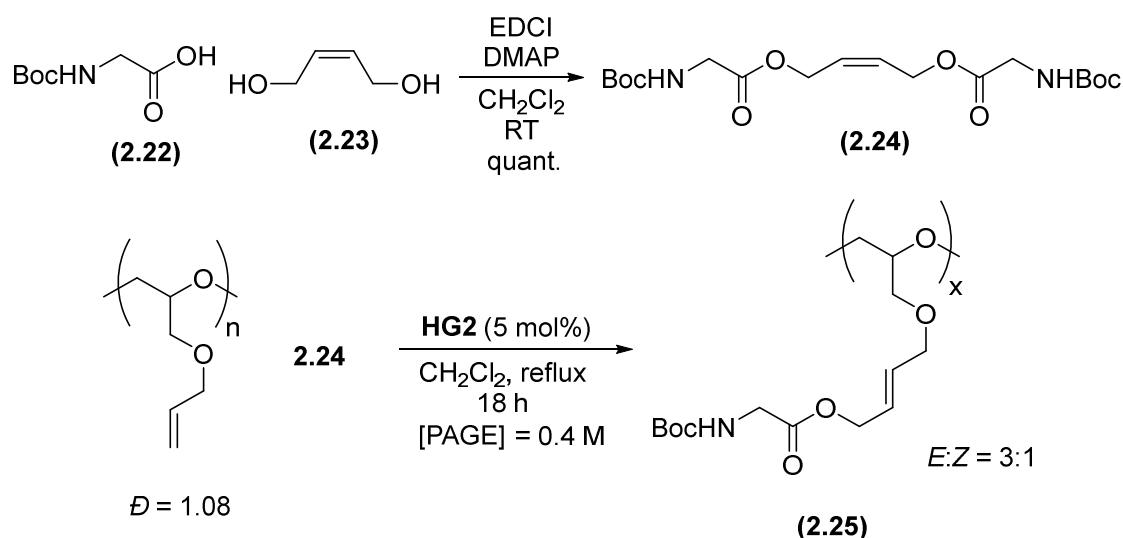
Scheme 2.13 – CM of PAGE with acrylamide derivatives

Entry	Coupling partner	x:y:z ^a	Yield ^b (%)
1	2.19	64:15:21	83
2	2.20	30:52:18	81
3	2.21	24:40:36	68

Table 2.7 - CM of PAGE with acrylamide derivatives. ^a x = PAGE-graft-X, y = unreacted PAGE, z = self metathesis. ^b calculated using adjusted molar mass (Equation 5).

2.6.3 CM using amino acids bearing C-terminus alkenes

It has been shown that allyl acetate dimer **2.4** was a good coupling partner for PAGE and so the same functional group was employed to place the olefin on the C-terminus of the amino acid. This was done by the esterification of Boc-Glycine-OH **2.22** with diol **2.23** using EDCI to furnish diester **2.24** in quantitative yield (Scheme 2.14). When **2.24** was subjected to CM with PAGE the conversion was 30%, compared to 95% when allyl acetate dimer **2.4** was used (**Table 2.8**, entry 1). Although this was a relatively low conversion, the ¹H-NMR of the coupled polymer was clean and possessed few of the unidentifiable signals that were common when acrylamides and allyl glycine derivatives were used. Additionally it was at this point that we acquired a GPC system, which allowed us to conduct dispersity analysis. The GPC elutogram indicated an increase in dispersity from 1.08 to 1.77, which was reflected in the ¹H-NMR indicating 70% rate of self metathesis. Additionally, we noticed that the reaction mixture was more viscous than previous CM reactions, which is likely due to the large molecular weight of **2.24**. We sought to reduce this viscosity by diluting the reaction from 0.4 M to 0.2 M, however this resulted in a decrease in conversion to 13% (entry 2). Whilst studying the coupling of PAGE with AA we had found that two sequential additions of **HG2** catalyst had resulted in high conversion, however when we implemented this method for coupling PAGE and **2.24** we noticed a slight decrease in conversion to 25%. Overall, we believe these low conversion may be due to the coupling partner being too large in size as to allow for efficient coupling to every pendent olefin of PAGE, yet too small in size as to act as effective steric hindrance to self metathesis of nearby PAGE chains. We decided to continue investigating other C-terminus allylic functionalised coupling partners, namely a bulky peptide that could potentially prevent intermolecular self metathesis.

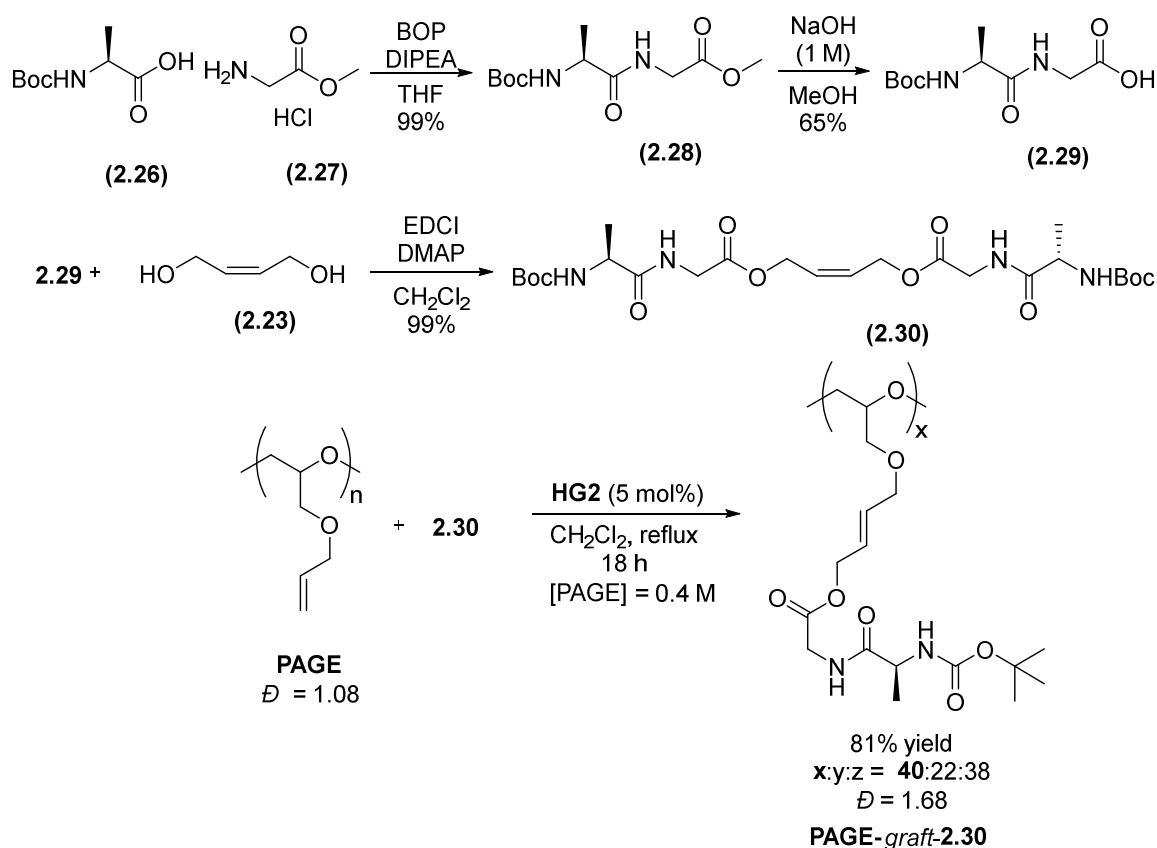


Scheme 2.14 – CM of PAGE with Boc-Gly-O-allyl

Entry	[2.24] mol/L	HG2 (mol%)	x:y:z ^a	\bar{D}	Yield ^b (%)
1	0.4	5	30:0:70	1.77	87
2	0.2	5	18:15:67	1.85	85
3	0.4 ^a	2 × 2.5	25:0:75	1.90	80

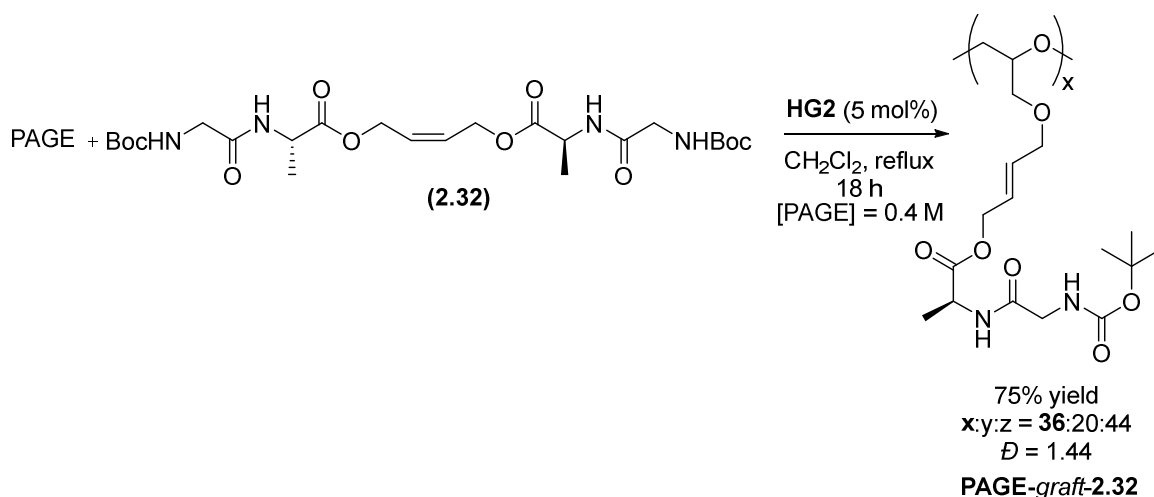
Table 2.8 - CM of PAGE with Boc-Gly-O-allyl. ^a x = PAGE-graft-X, y = unreacted PAGE, z = self metathesis. ^b calculated using adjusted molar mass (Equation 5).

As well as potentially preventing self metathesis, coupling peptides to PAGE was also part of our overall goal. This was first done using a dipeptide of alanine **2.26** and glycine **2.27**, which were coupled together using BOP to produce the methyl ester Boc-Ala-Gly-OMe **2.28** that was then hydrolysed using NaOH in methanol to yield the free acid **2.29** (Scheme 2.16). Upon esterification with diol **2.23**, the diester **2.30** was achieved in 99% yield. CM with PAGE resulted in a conversion of 40%, although interestingly the remaining repeating units had not all undergone self metathesis, rather 22% of repeating units were left unchanged as the allyl group and 38% had shown self metathesis. This indicated that the increased size of a peptide, as compared to amino acid residues, was possibly sterically hindering the unreacted allyl handles from self metathesis, a theory that is supported by Meier *et al*, whose work showed that increasing size of acrylate esters lead to lower occurrences of self metathesis.^[63] GPC analysis also indicated self metathesis with an increase in dispersity from 1.08 to 1.68, a slight improvement than when PAGE was coupled to amino acid **2.24**.



Scheme 2.15 - Synthesis of dipeptide Boc-Ala-Gly-O-allyl dimer and subsequent CM with PAGE

We were also interested to see how placing the alanine closer to the alkene may affect the conversion with PAGE (Scheme 2.16). The hypothesis was that with alanine being closer in space to the olefin, there may be a decrease in the conversion of coupling onto the polymer backbone. After CM a conversion of 36% was observed (compared to 40% for **2.30**), indicating that the methyl group may play a role in shielding the polymer from successive CM. However, this may well be within experimental error as the CM was only attempted once. Dispersity showed an increase from 1.08 to 1.44 indicating that self metathesis was not as prevalent as when PAGE was coupled with **2.30**.

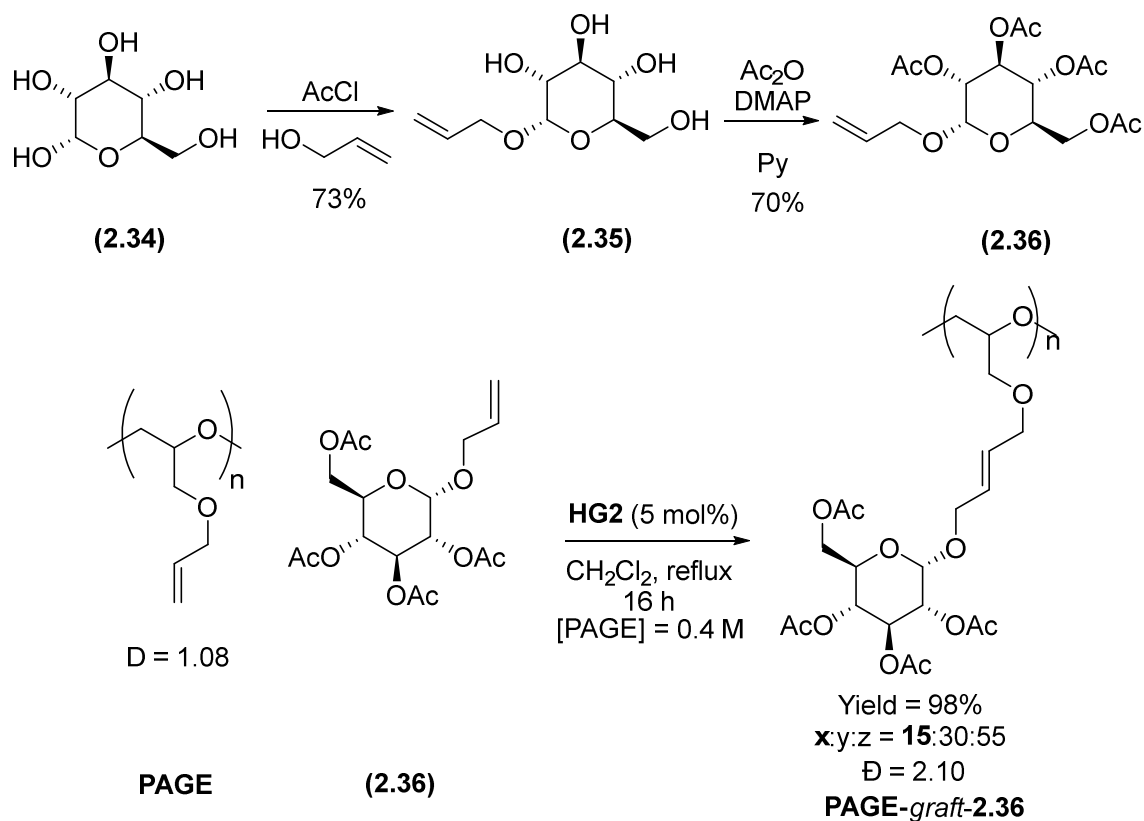


Scheme 2.16 - Synthesis of dipeptide Boc-Gly-Ala-O-allyl dimer and subsequent CM with PAGE

Overall, we found that C-terminus functionalised peptides did not allow for the high levels of conversion that we obtained with smaller simpler molecules such as MA and AA. However it should be noted that the C-terminus alkenes yielded a much cleaner polymer with less unidentifiable side reactions that were prevalent when allyl glycine and acrylamides were used. At this point, we were interested to investigate how the size of the coupling partner influences the successful conversion when coupled to PAGE.

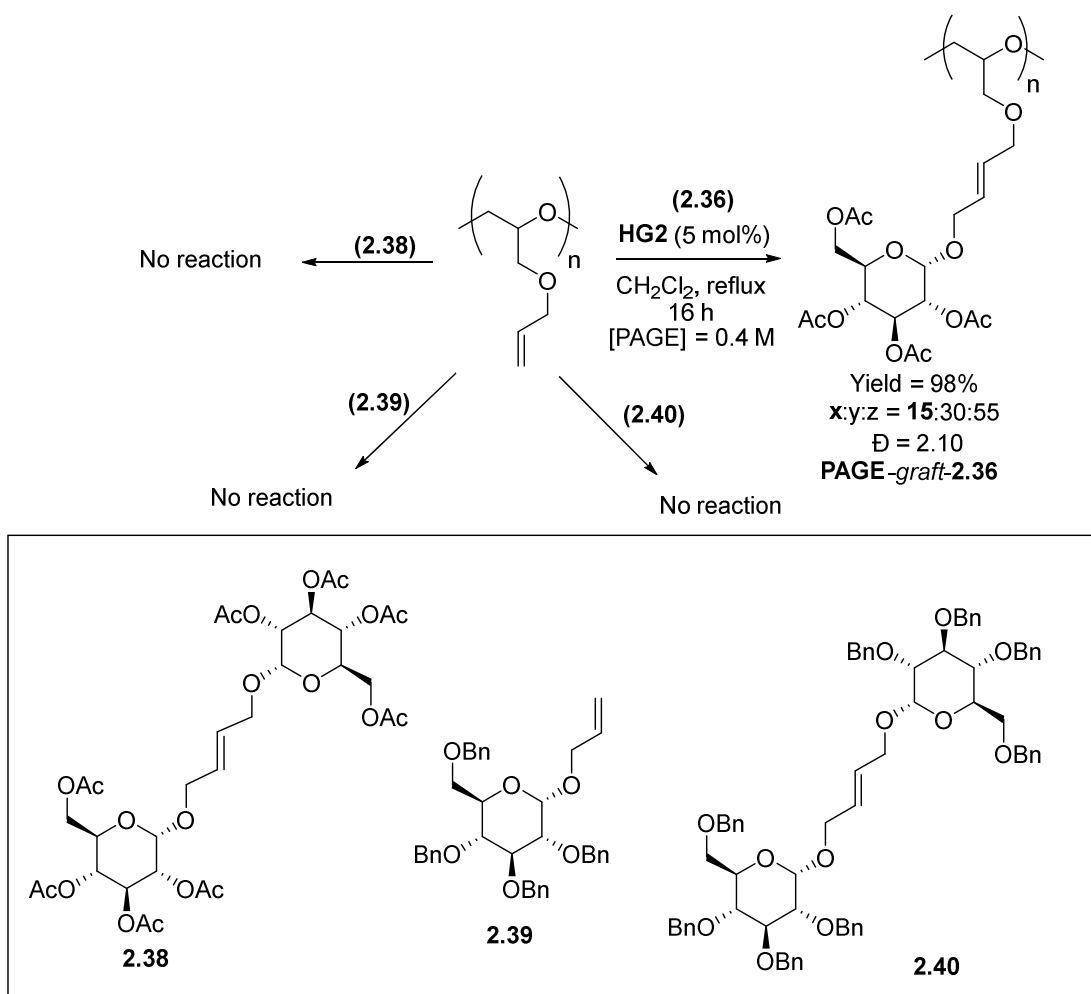
2.7 Influence of the size of the coupling partner on CM

Results to this point were implying that the size of the coupling partner played a vital role in determining the conversion of the CM reaction, and additionally influencing the degree of self metathesis observed. This was an issue that would certainly become important when the project moved towards the goal of coupling the PAGE with large biomolecules such as Taxol or RGD. In order to study the effect of coupling size, some simple biomolecules were studied.



Scheme 2.17 - CM of PAGE with allyl glucose

The first sterically encumbered molecule chosen as a model substrate was allyl glucose derivative **2.36**, as it was inexpensive and possessed no functional groups that would interfere with the CM reaction. This coupling partner was produced by allylation of glucose at the anomeric position to yield **2.35** followed by acetylation of the remaining hydroxyl groups using acetic anhydride. This peracetylation was necessary in order for the glucose derivative to be soluble in dichloromethane for the CM with PAGE (Scheme 2.17). As expected the conversion was low at 15%, but the residual allyl repeating units was 30%. High degrees of self metathesis (55%) were expected due to the type 1 nature of the coupling partner, which have previously been explained to be troublesome in CM reactions. CM of **2.36** with **HG2** yielded dimer **2.38**, which was then and subjected to CM with PAGE. Unfortunately no conversion was achieved and only cross linked polymer was recovered. This is most likely due to large steric hindrance around the disubstituted olefin of the glucose dimer **2.38**. The larger benzylated glucose compounds **2.39** and **2.40** were also synthesised and subjected to CM with PAGE, however these species also showed no evidence of successful coupling, with mostly self metathesis being observed (**Scheme 2.18**).



Scheme 2.18 - CM with glucose derivatives. Reaction conditions **HG2** (5 mol%, CH_2Cl_2 , 45 °C, 18 h)

Overall the only successful conversion we observed was with the homodimer of acetylated glucose **2.36**, which coupled to PAGE with the retention of 30% of polymer allyl handles. This retention of the allyl groups could be due to deactivation of the ruthenium catalyst, which we had suggested when we observed poor coupling of the acrylamides to PAGE, however due to the lack of functional groups in this case we propose two alternative explanations.

Scenario A. the large size the coupling partner sterically hinders other polymer chains from coming into contact with a polymer strand, thereby limiting self metathesis and retaining the allyl handle intact.

Scenario B. unsuccessful coupling of PAGE with **2.36** allows for self-metathesis to occur in a predominantly intramolecular fashion to yield a globular particle. These structures could possess a folded conformation with residual pendent allyl handles located internally, allowing them to be shielded from the reaction media, and thus left intact.

Scenario A would be justifiable had we achieved moderate conversion, however 15% conversion seems too low to have any real effect on preventing polymer strands from

coming into proximity with one another. Scenario B seemed like the most likely since production of *Z*-alkenes (indicative of intramolecular self metathesis) was something that we had previously observed when optimising reaction conditions for coupling PAGE with MA. Unfortunately due to the high levels of self metathesis of **PAGE-graft-3.26**, the ¹H-NMR showed a broad singlet, preventing us from using coupling constants to conclude whether the self metathesis was intramolecular or intermolecular. However GPC analysis indicated a large increase in dispersity from 1.08 to 2.10 indicating significant intermolecular cross linking.

Overall, it is likely that the self metathesis we saw was a combination of both intramolecular and intermolecular homodimerisation, and so we were not able to conclude at this point whether the size of coupling partner played a vital role in preventing self metathesis.

2.8 Conclusion

Synthesis of PAGE was achieved using potassium metal, naphthalene and benzyl alcohol, to produce polymer in $M_n = 7,990 \text{ g.mol}^{-1}$ and $\bar{D} = 1.08$. Optimal conditions for the coupling of MA (type 2) to PAGE were sought, and we found that relatively high concentration (0.4 M) was required to achieve conversion of 98%. Allyl acetate was also investigated as a model coupling partner for type 1 analogues. Unfortunately low conversions were observed for AA, however upon use of the preformed **Z-2.3**, we were able to obtain the desired graft polymer in 98% conversion.

Coupling of amino acids to PAGE were also investigated. Use of allyl glycine derivatives as well as various acrylamides resulted in poor conversion and unidentifiable side reactions. Although C-terminus ally esters only offered a moderate conversion of ~30%, it should be noted that the grafted polymers were significantly cleaner. Ultimately, we achieved coupling of dipeptides **2.30** and **2.32**, which is a positive step towards coupling tripeptide RGD.

Investigation into the use of a bulky coupling partner was disappointing as it did not appear to suppress self metathesis as we had intended. Due to broadening of the ¹H-NMR spectrum is unclear whether self metathesis is predominantly occurring inter or intramolecularly. Retention of pendent olefin handles indicate the possible formation of a folded conformation, formed by intramolecular self metathesis, however significant increases in dispersity suggest intermolecular homodimerisation is present. Therefore, we suspect the self metathesis that is present in many couplings with PAGE it is a combination of both intramolecular and intermolecular processes.

Chapter 3 : Synthesis of polymer range PAGE, PCGE, PPGE, PMAGE

This chapter will discuss the synthesis of a new range of polymers that are intended to reduce the degree of self metathesis, and thus improve the dispersity of the conjugated polymers. Cross metathesis will then be carried out on these polymers with the ultimate goal of attaching cell targeting tripeptide RGD. Focus will then be shifted to the synthesis of various copolymers, which would enable to bifunctionalisation of the PEG chain. This would be of particular interest when synthesising a polymer conjugate that contains both a drug and a cell targeting moiety such as RGD.

3.1 New approach to prevent self metathesis of the polymer during CM

It was decided at this point in time that the self metathesis of the polymer was a problem that could not be solved by only adjusting reaction conditions or using specific coupling partners. Therefore, we decided to synthesise a range of new polymers that were naturally less likely to undergo self metathesis.

As described by Grubbs *et al.*, olefins can be categorised into one of four types according to their rate of homodimerisation in the presence of a specific catalyst.^[53] We proposed that by changing the type of alkene present on the polymer, we could control the degree of self metathesis, allowing for a more monodisperse product to be formed. The polymers proposed are shown in Figure 3.1.

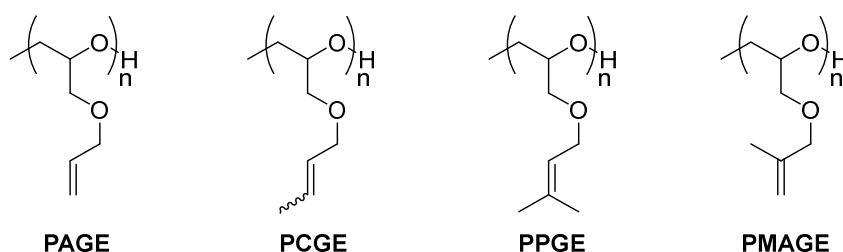
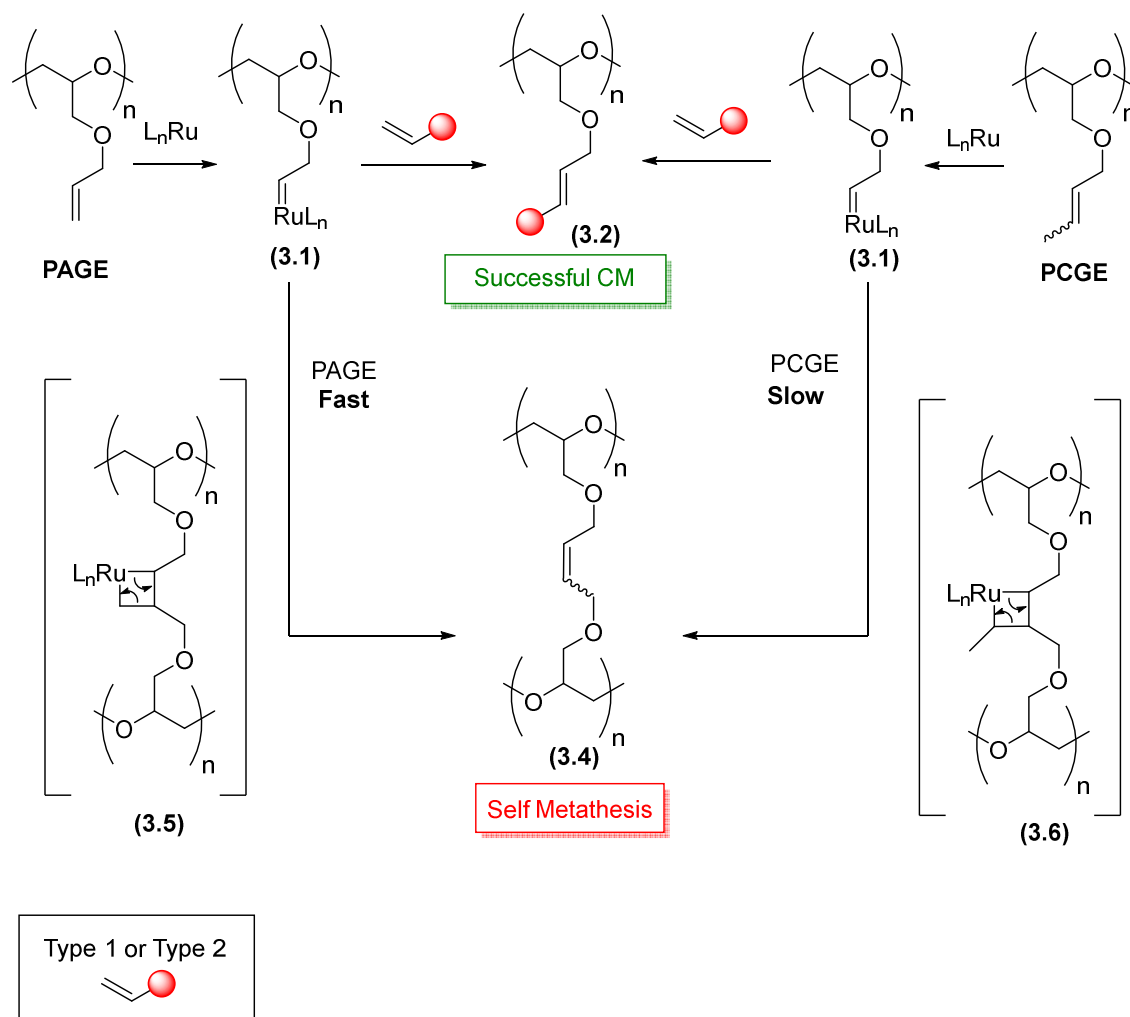


Figure 3.1 - New polymer range with varying olefin reactivity.

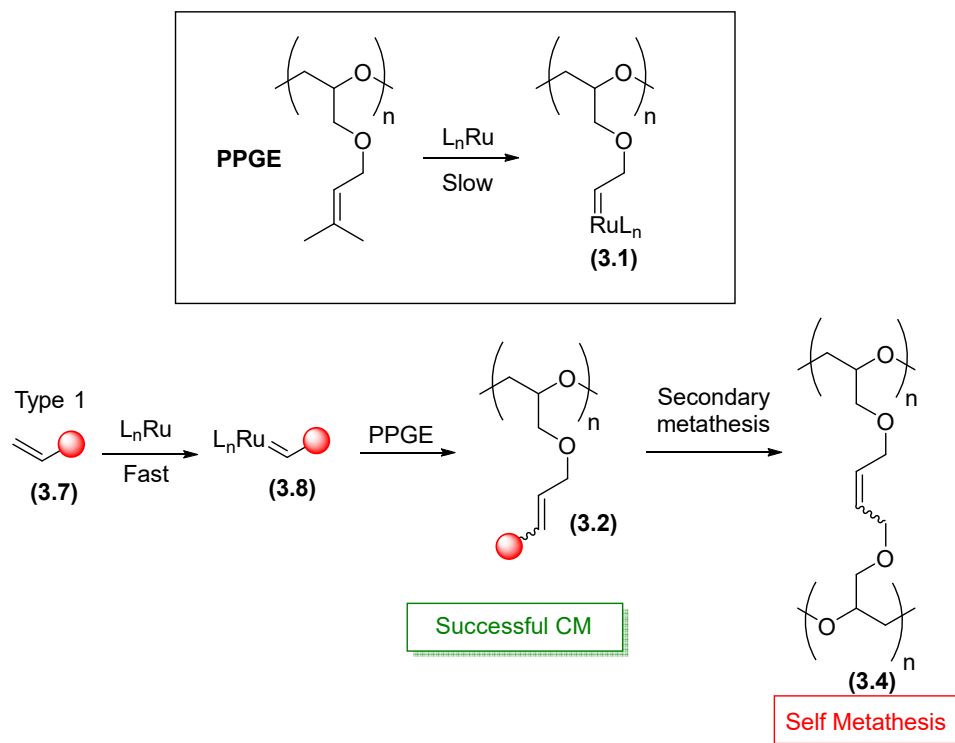
As previously stated, poly(allyl glycidyl ether), PAGE is a type 1 olefin and although it is capable of coupling with less reactive coupling partners such as MA, it has been shown to readily homodimerise to yield a cross linked polymer. When a type 2 coupling partner such as **MA** is used, the ruthenium catalyst should react primarily with allyl handle of PAGE to form the metal-polymer alkylidene complex **3.1**, which would then react readily with another pendent type 1 group, yielding a SM product **3.4** (Scheme 3.1). Homodimerisation can be prevented to some degree by using high equivalents of coupling partner, however, as our work with MA and AA proved, this cannot entirely prevent this undesirable homodimerisation.

Poly(crotyl glycidyl ether), PCGE is also type 1 olefin that should show good reactivity towards metathesis; however it should be less likely to undergo self metathesis than PAGE. Under CM conditions, the ruthenium catalyst will first undergo a [2+2] cycloaddition with the crotyl handle PCGE to form the metal-polymer alkylidene complex **3.1**, as it did with PAGE, however this alkylidene complex should have a decreased propensity for subsequent homodimerisation than when PAGE was used. This is due the methyl group of the crotyl handle creating an increase in steric hindrance around the four-membered transition state **3.6**, which is not present in the homodimerisation of PAGE (Scheme 3.1). Overall, PCGE should offer a decrease in the rate of homodimerisation, whilst maintaining sufficient reactivity to coupling partners such as MA.



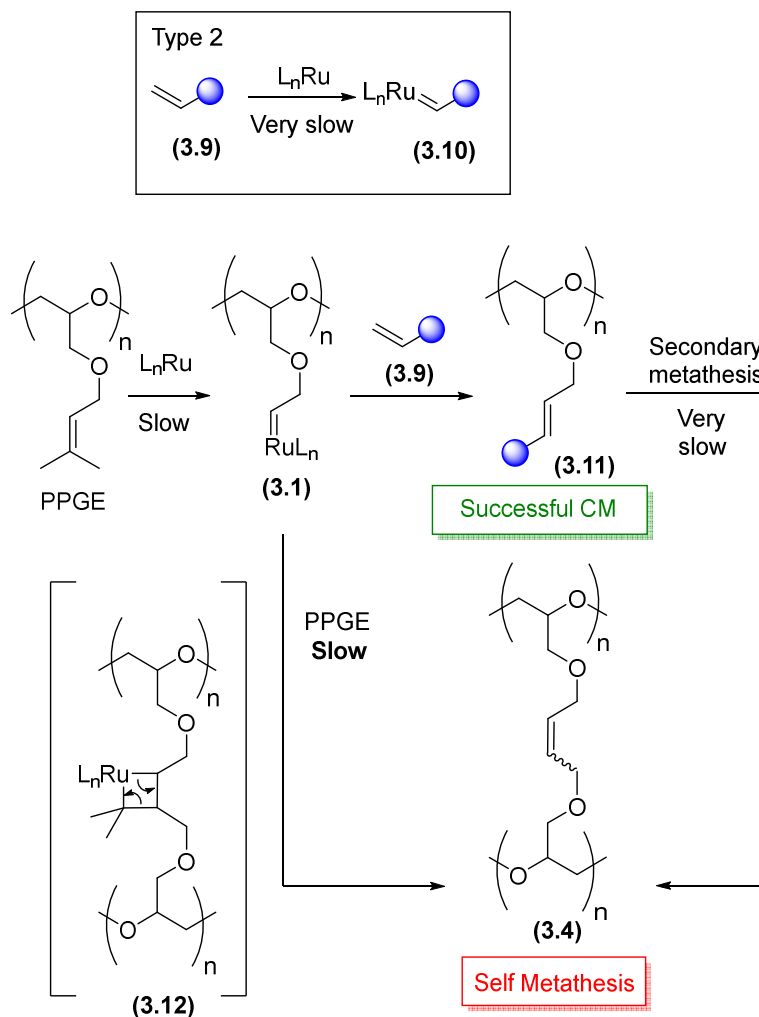
Scheme 3.1 – Reaction pathway for the conjugation of PAGE and PCGE using CM.

Poly(prenyl glycidyl ether), PPGE is type 2 in nature, and therefore the pathway towards successful conjugation should be highly dependent on the type of coupling partner used. In the case of coupling with a type 1 coupling partner, self metathesis of PPGE should occur to a much lesser degree than in the case of PCGE or PAGE, as the trisubstituted olefin should be less likely to form the metal-polymer alkylidene intermediate **3.1** that is necessary for self metathesis (Scheme 3.2). Instead, the ruthenium catalyst should react principally with the type 1 coupling partner **3.7** before reacting with the PPGE. This final coupling of **3.8** with PPGE would be slow due to the trisubstituted nature of the prenyl olefin, however a low conversion with no self metathesis that allows for retention in monodispersity may potentially be favourable over a polymer that results in high self metathesis. A possible pitfall of PPGE may be subsequent secondary self metathesis of conjugated polymer **3.2** to form **3.4**. Time may prove to be an important factor in preventing this secondary metathesis from producing high degree of self metathesis.



Scheme 3.2 - Reaction pathway for the conjugation of PPGE with type 1 coupling partner.

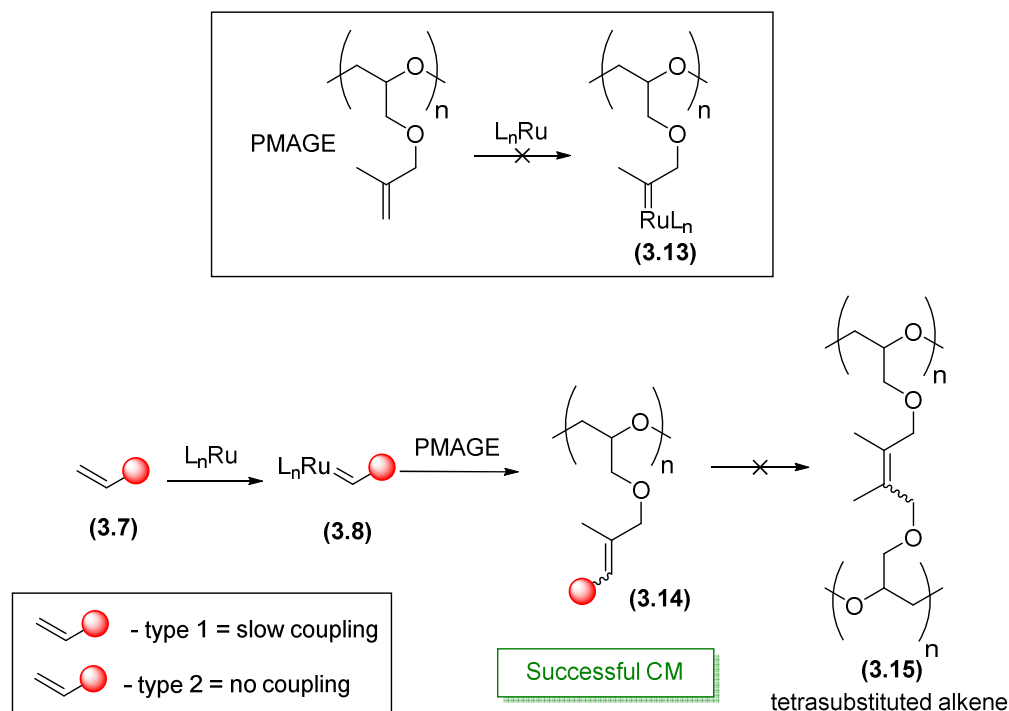
In the case of coupling a type 2 species with PPGE, we believe that, due to the unreactive coupling partner **3.9** being unlikely to form an alkylidene intermediate **3.10**, the ruthenium catalyst would react principally with the prenyl olefin of PPGE (Scheme 3.3). This may occur relatively slowly due to the trisubstituted nature of the alkene, however should eventually occur, leading to form polymer-ruthenium carbene **3.1**. Self metathesis could occur at this point, however due to the high energy of the dimethyl substituted 4-membered ring intermediate **3.12**, it is more likely that **3.1** would undergo CM with coupling partner **3.9** to yield the desired functionalised polymer **3.11**. Interestingly, when coupling partner **3.9** is electron deficient, the final product **3.11** should be stable and unlikely to undergo secondary CM that could lead to self metathesis product **3.4**.



Scheme 3.3 - Reaction pathway for the conjugation of PPGE with type 2 coupling partner.

Poly(methallyl glycidyl ether), PMAGE is a type 3 *gem*-disubstituted olefin like PCGE however its capability to undergo self metathesis should be minimal as homodimerisation would result in a tetrasubstituted (type 4) olefin **3.15**, which is not possible under typical CM conditions (Scheme 3.4). The reaction pathway should start with the ruthenium catalyst reacting with the coupling partner **3.7** (type 1) to yield alkylidene intermediate **3.8**, which would then undergo CM with PMAGE to produce **3.14** (Scheme 3.4). When a type 2 olefin is reacted with PMAGE there should be no observable coupling, as both the formation of carbene **3.10**, and the subsequent coupling to PMAGE would be very slow, leading to minimal successful coupling to PMAGE.

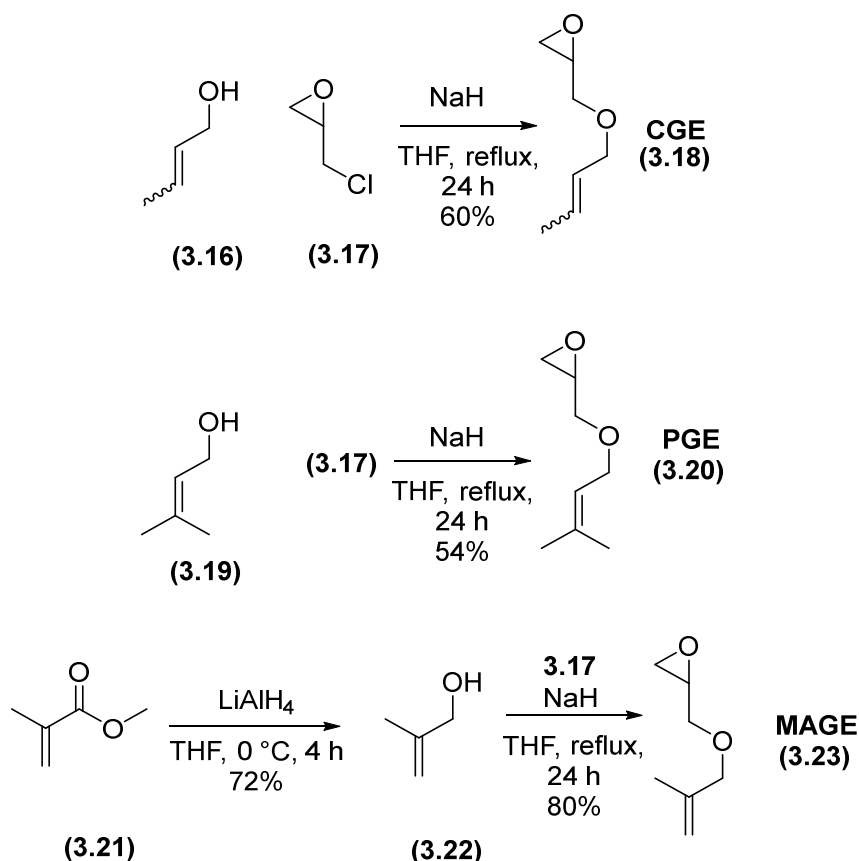
Overall, even though PMAGE possesses a type 3 olefin, which may make full conversion difficult, the absence of any pathway leading to the self metathesis **3.15**, makes PMAGE a very interesting candidate for functionalisation.



Scheme 3.4 - Reaction pathway for the conjugation of PMAGE using CM.

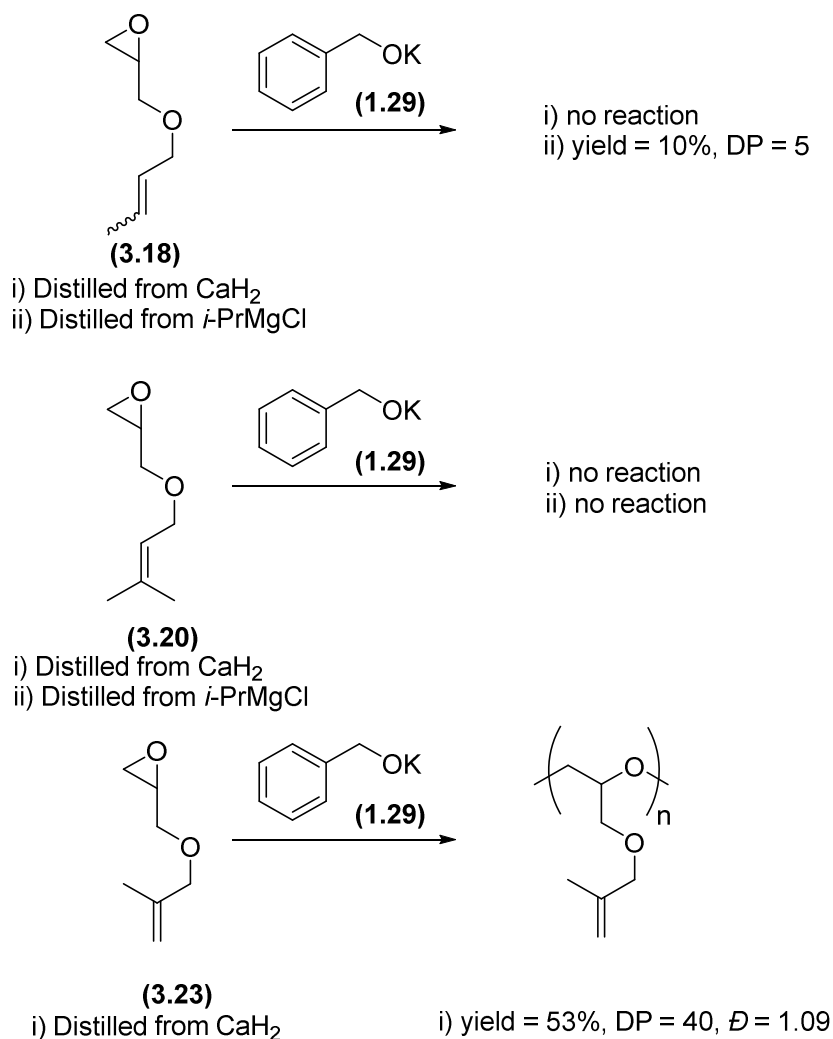
3.2 Synthesis of PAGE, PCGE, PPGE, PMAGE

Synthesis of the monomers CGE, PGE, and MAGE ethers was achieved by the $\text{S}_{\text{N}}2/\text{S}_{\text{N}}2'$ reaction of racemic epichlorohydrin with the crotyl, prenyl, and methylallyl alcohols respectively. The reaction could also occur by nucleophilic attack of the epoxide followed by intramolecular displacement of the chlorine which would also furnish the same product (Scheme 3.5). Obtaining a pure monomer product was of paramount importance, as anionic ROP is extremely sensitive to protic species such as alcohol **3.16**, **3.19**, and **3.22**, as well as electrophiles such as epichlorohydrin **3.17**. Due to both epichlorohydrin and alcohols **3.16**, **3.19**, and **3.22** possessing similar boiling point to the monomer products **3.18**, **3.20**, and **3.23**, it was difficult to obtain a pure product using only distillation. For this reason, excess alcohol was used in the coupling, as this polar starting material was more easily removed during column chromatography. Additionally, the relatively volatile monomers required careful handling to prevent loss by evaporation.



Scheme 3.5 – Synthesis of monomers CGE, PGE, MAGE.

Polymerisation of the monomers **3.18**, **3.20**, and **3.23** was then attempted using potassium benzoxide **1.29** under conditions previously used to achieve the synthesis of PAGE. Unfortunately, only MAGE monomer **3.23** successfully underwent polymerisation (yield = 53%, DP = 40, \bar{D} = 1.09), with CGE and PGE returning only starting material (Scheme 3.6). Initially, we believed that this was due to residual epichlorohydrin left over from the monomer synthesis. Therefore, we moved from distilling the monomer from CaH_2 , to distilling it from isopropyl magnesium chloride as the increased nucleophilicity of $i\text{-PrMgCl}$ should aid the removal of the electrophilic impurity. In the case of CGE, this change in purification allowed for sufficiently pure monomer that could undergo polymerisation in 10% yield, however the DP was very low (DP = 5). Due to the low molecular weight of the obtained polymer, it was not possible to measure the dispersity using GPC as it was out with the range of the column (1,000 – 40,000 Da). Additionally, without the use of a glove box to handle potassium we were concerned that the preparation of initiator **1.29** was allowing for the incorporation of moisture to the reaction.

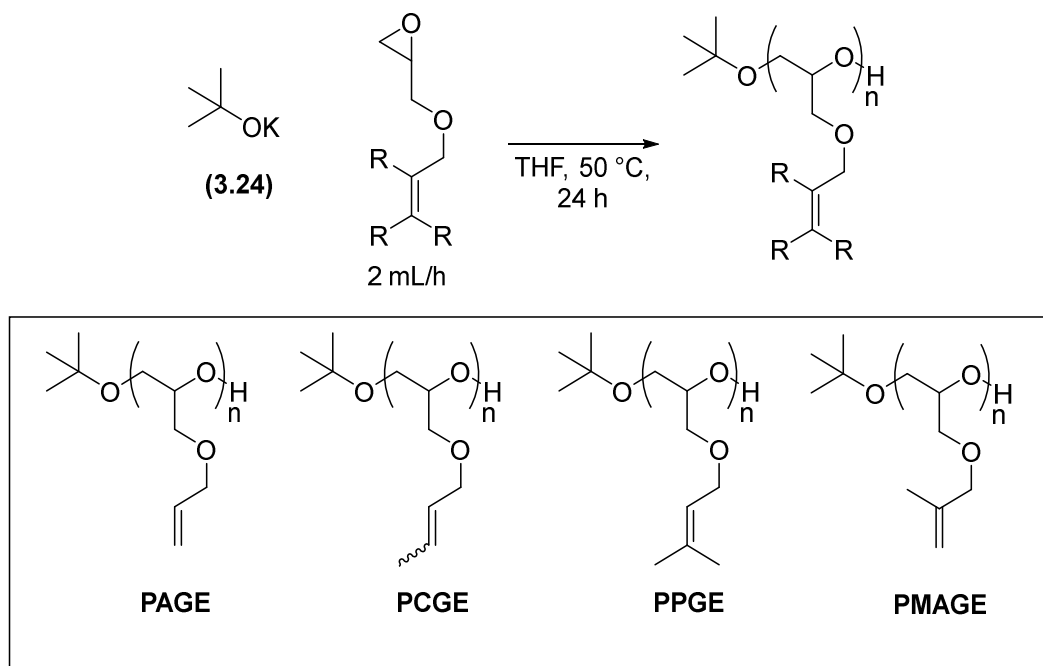


Scheme 3.6 – Polymerisation of CGE, PGE and MAGE monomers using potassium benzoxide.

Fortunately, at this point we read of a recent development by Groll *et al.* allowing for the facile synthesis of PAGE in controlled dispersity by the slow addition of the AGE monomer to potassium *tert*-butoxide initiator **3.24**, as discussed in Section 1.3.2.^[38] Slow addition of the monomer at $2 \text{ mL}\cdot\text{h}^{-1}$ over 4 hours to *t*-BuOK **3.24** in THF allowed for the successful production of a quasi-monodisperse polymers (Scheme 3.7). Unlike the previous synthesis developed of PAGE using benzyl alkoxide **1.29** by C. Hawker, which required the removal of THF solvent prior to the addition of monomer, this new method worked well with the THF still present. This is likely due to the commercially supplied *t*-BuOK **3.24** in THF possessing less protic impurities than the manual synthesis of benzyl alkoxide **1.29**.

Polymers were synthesised with a target $M_n > 10,000 \text{ g}\cdot\text{mol}^{-1}$, which was achieved for all four polymers. Hawker *et al.* had reported instances of olefin isomerisation during the synthesis of PAGE, however fortunately we did not observe any occurrence of this during the synthesis of PAGE, PCGE, PPGE, or PMAGE.^[37]

Acceptable dispersity was also obtained for all polymers, however PPGE possessed a dispersity of 1.38. We repeated this polymerisation but the second batch of PPGE showed similarly higher dispersity. Due to the lack of isomerisation that would occur by chain termination (Scheme 1.5), we suggest that this occurrence of high dispersity must be due to residual protic impurities left over from the synthesis of PGE. Although this relatively high dispersity was not ideal, we were interested principally in the *change* in dispersity upon coupling by CM, therefore decided to proceed with the coupling of the new polymer range with various small molecules.



Scheme 3.7 - New polymer range using slow addition method by Groll *et al.*^[38]

Entry	Monomer ^a	Yield (%)	Mn ^b (g/mol)	Mn ^c (g/mol)	Mw ^c (g/mol)	Mn (theoretical)	Đ ^c
1	AGE	99	10773	10009	11620	11400	1.16
2	CGE	85	14970	9166	11443	12800	1.25
3	PGE	90	13380	9980	13778	14200	1.38
4	MAGE	98	13250	15849	18239	12800	1.15

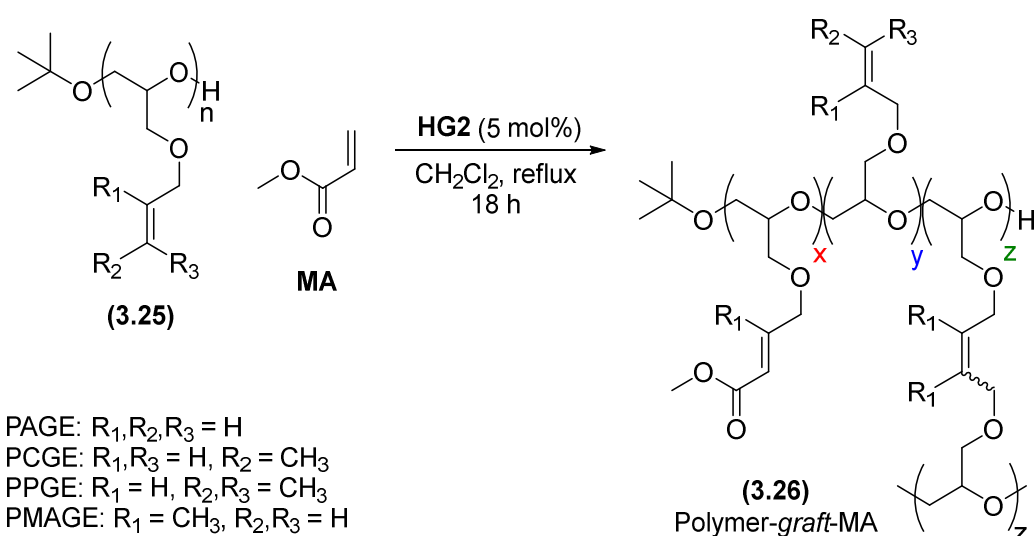
Table 3.1 - Synthesised polymer range. ^a Monomer added at 2 mL.h⁻¹ and reactions performed at 50 °C, 24 h. ^b Determined by ¹H-NMR. ^c Determined by GPC analysis.

3.3 Cross Metathesis with PAGE, PCGE, PPGE, and PMAGE

Coupling of PAGE to various small molecule olefins as described in chapter 2 included MA, AA, and amino acids. We then applied the same reaction conditions to the new polymer range of PAGE, PCGE, PPGE, and PMAGE.

3.3.1 CM with MA

Using the optimised conditions from Chapter 2, we repeated the CM of PAGE with MA (Scheme 3.8)



Scheme 3.8 - CM of PAGE, PCGE, PPGE and PMAGE with MA.

We were surprised that the new polymer of (*t*-BuO)-PAGE (synthesised with *t*-BuOK initiator **3.24**) only achieved 85% conversion compared to 98% with the previous polymer (BnO)-PAGE (synthesised by benzyl alkoxide initiator **1.29**) (Entry 1, Table 3.2). The differences between polymers (BnO)-PAGE and (*t*-BuO)-PAGE are in M_n (~8 kDa and ~11 kDa respectively) and dispersity (1.08 and 1.16 respectively) (Figure 3.2). Considering the identical nature of the pendent allyl olefins in both polymers, the difference in conversion must due to the macromolecular structure of these polymers. (*t*-BuO)-PAGE possesses a higher M_n , which means that the number of (*t*-BuO)-PAGE molecules, per mol of allyl groups, is lower than in (BnO)-PAGE. A diagrammatic example of this is shown in Figure 3.2, whereby each polymer could have an equal number of allyl groups, but difference number of molecules. This increases the chances of (*t*-BuO)-PAGE undergoing intramolecular self metathesis, leading to a folded polymer than shields the internal

macrostructure from the reaction media, thereby limiting access of MA to the residual allyl handles of the polymer.

Note that from now on (chapter 3 and 4), unless otherwise stated, any mention to PAGE is referring to (*t*-BuO)-PAGE ($M_n \sim 11$ kDa, $\bar{D} = 1.16$).

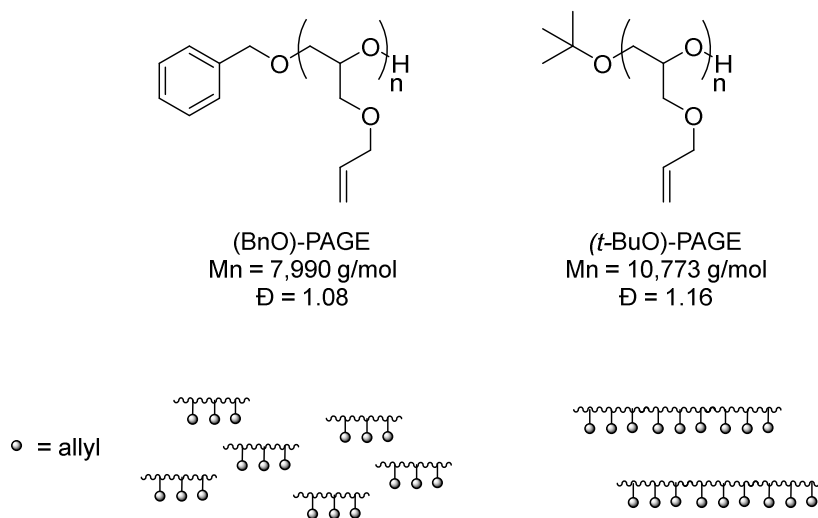


Figure 3.2 – Comparison of both PAGE polymers.

Coupling of PCGE with methyl acrylate saw a slight decrease in conversion in comparison to PAGE (80% and 85% respectively), with an overall increase in self metathesis, indicating that the added methyl group in the four membered transition state was not inhibiting the formation of the SM product (entry 2).

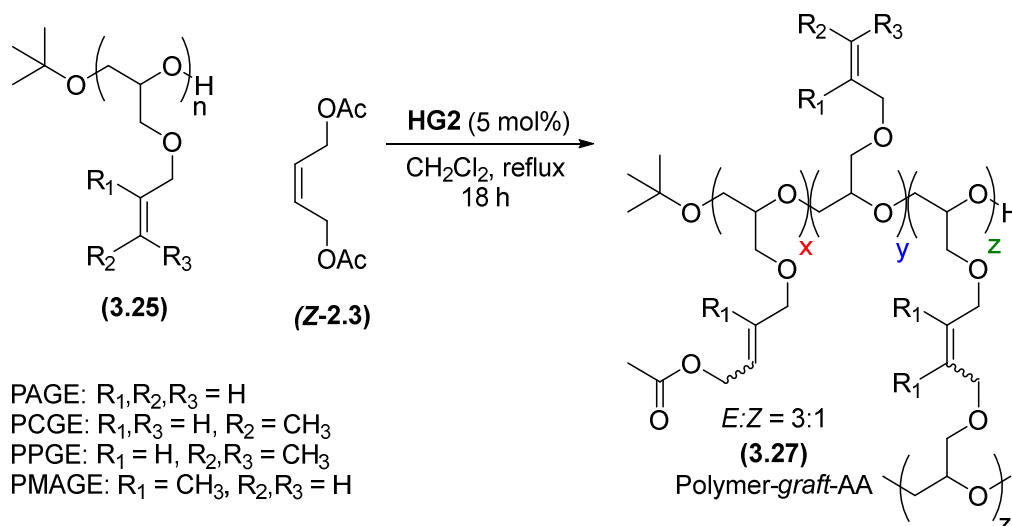
The reaction of PPGE with MA saw a significant increase in conversion to 95% with a significant drop in self metathesis to 3% (entry 3), which is likely due to the increased strain around the 4-membered intermediate **3.12** limiting the homodimerisation of the pendent prenyl handle. Additionally, although the self metathesis decreased significantly, the dispersity increased to 2.00, which supports the idea that even a small amount of self metathesis can result in a polydisperse product. Unsurprisingly, use of PMAGE saw no conversion with MA due to the low reactivity of the pendent type 3 olefin.

		Conversion (x) ^a	Unreacted (y) ^a	Self Metathesis (z) ^a	\bar{D} before ^b	\bar{D} after ^b	Yield (%)
Entry 1	PAGE	85	5	10	1.16	2.11	92
Entry 2	PCGE	80	0	20	1.25	2.21	95
Entry 3	PPGE	95	2	3	1.38	2.00	84
Entry 4	PMAGE	0	100	0	1.15	-	-

Table 3.2 - CM of polymer range with MA. ^a Determined by ¹H-NMR integration. x,y,z relate to Scheme 3.8. ^b Measured by GPC.

3.3.2 CM with AA

Previous work using (BnO)-PAGE had shown the *Z*-alkene dimer **Z-2.3** to be the optimal coupling partner for grafting allyl acetate onto the polymer backbone, and so **Z-2.3** was investigated as a model type 1 coupling partner for the new polymer range.



Scheme 3.9 - CM of PAGE, PCGE, PPGE, and PMAGE with AA.

Coupling of **Z-2.3** with (*t*-BuO)-PAGE resulted in a decrease in conversion in comparison to the previous polymer (BnO)-PAGE (Table 3.3). As discussed in Section 3.3.1 we believe that the increase in M_n leads to a greater propensity to undergo self metathesis. This was accompanied by an increase in dispersity from 1.16 to 1.46. Unfortunately neither PCGE, PPGE or PMAGE offered greater conversion, however interestingly, PMAGE underwent 23% conversion with no evidence of SM. This absence of self metathesis was reflected in the dispersity which decreased slightly from 1.15 to 1.09 (entry 4).

		Conversion (x) ^a	Unreacted (y) ^a	Self Metathesis (z) ^a	\bar{D} before ^b	\bar{D} after ^b	Yield (%)
Entry 1	PAGE	87	4	9	1.16	1.46	90
Entry 2	PCGE	73	12	15	1.25	1.98	83
Entry 3	PPGE	60	30	10	1.38	1.76	95
Entry 4	PMAGE	23	77	0	1.15	1.09	95

Table 3.3 - CM of polymer range with AA. ^a Determined by ^1H -NMR integration. x,y,z relate to Scheme 3.9. ^b Measured by GPC.

Up to this point we had found PMAGE to be the best candidate for CM, as it offered no self metathesis pathway, however there is a limitation in the obtainable conversion, due to the unreactivity of the olefin of the polymer. As a result, we then focused on finding the optimal conditions to achieve high conversion with PMAGE by varying the reaction conditions for CM. This was done by varying solvent and temperature (Table 3.4).

Changing the solvent from CH₂Cl₂ to 1,2-dichloroethane (entry 2) yielded an identical polymer, however use of toluene at the same temperature increased the conversion from 23% to 41% (entry 3). It has been documented in the literature that the initiation of **HG2** catalyst, whereby the isopropoxystyrene dissociates from the ruthenium complex, occurs much faster in toluene than in CH₂Cl₂.^[110] Due to the unreactive nature of PMAGE, this increase in the initiation of **HG2** must play a crucial role in allowing for high conversion of the polymer with **Z-2.3**.

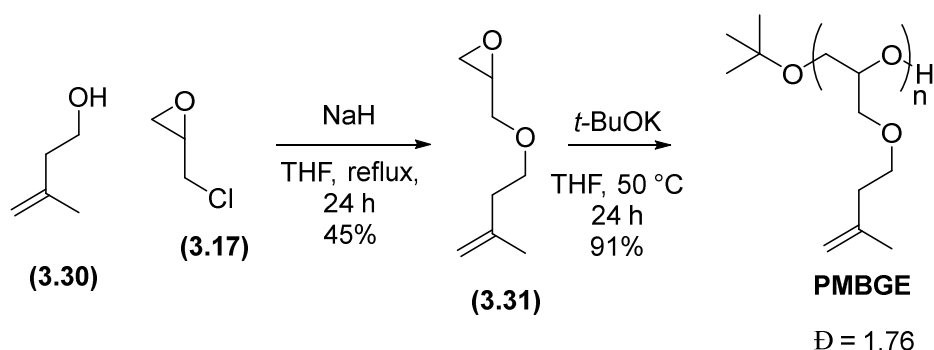
Surprisingly, increasing the temperature to 85 °C while using 1,2-dichloroethane did not result in an increase in conversion (entry 4), however switching to toluene at this elevated temperature resulted in a further increase in conversion to 50% (entry 5). Pushing the reaction conditions to employ refluxing toluene did not result in further conversion (entry 6). It is possible that when 50% conversion is reached, the steric hindrance around the polymer backbone is the limiting factor, as opposed to unreactivity of the *gem*-disubstituted olefin. This plateauing of the conversion is exemplified when the time is increased to 48 h, which sees the conversion remain steady at 48% (entry 7).

Entry	Solvent	Temperature (°C)	Conversion ^b	Yield
1	CH ₂ Cl ₂	45	23	98
2	C ₂ H ₄ Cl ₂	45	23	96
3	Toluene	45	41	98
4	C ₂ H ₄ Cl ₂	85	23	98
5	Toluene	85	50	97
6	Toluene	110	47	99
7 ^a	Toluene	110	48	99

Table 3.4 - CM of PMAGE with **Z-2.3** with various temperature and solvents ^a All reactions performed over 18 h, except entry 7, which was performed over 48 h. ^b Determined by ¹H NMR integration.

Results of the coupling of PMAGE with **Z-2.3** had indicated that conversion was limited to ~50%, which may be caused by steric hindrance around the polymer backbone. In order to investigate this, we envisaged the synthesis of poly(methylbutenyl glycidyl ether), PMBGE,

which possesses a *gem*-disubstituted alkene, and would therefore not undergo self metathesis, however with a pendent olefin that is slightly further away from the polymer backbone (Scheme 3.10). Synthesis of PMBGE started with the coupling of 3-methyl-3-butene-1-ol **3.30** with epichlorohydrin **3.17** to yield monomer MBGE, which was then slowly added to *t*-BuOK to furnish PMBGE with a dispersity of 1.76.

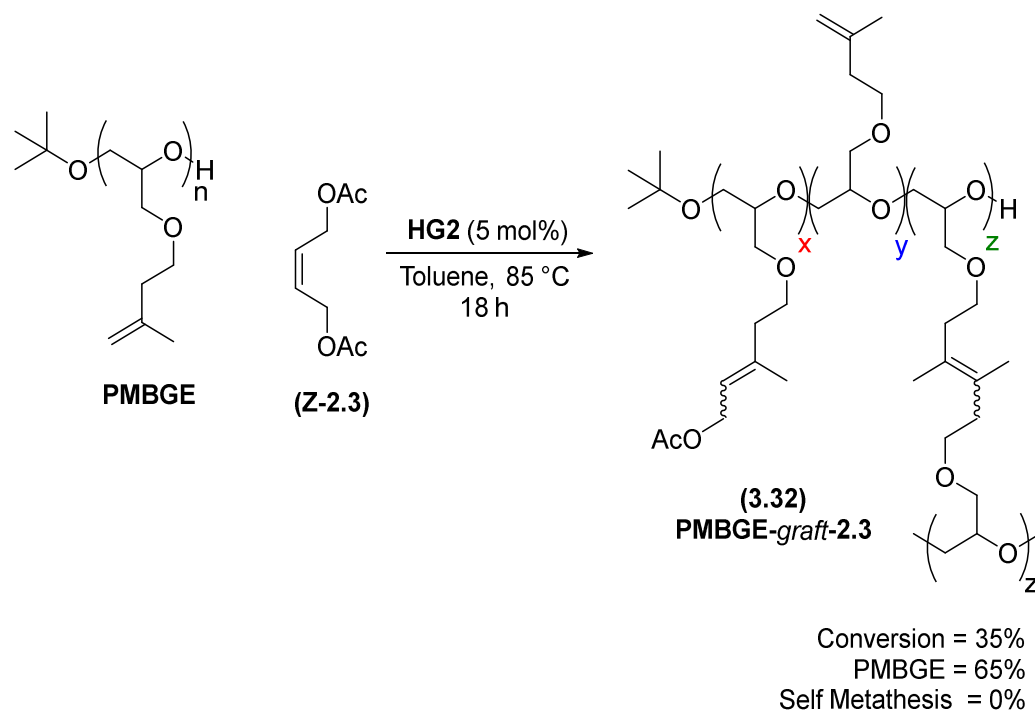


Scheme 3.10 – Synthesis of PMBGE

Monomer ^a	Yield (%)	Mn ^b (g/mol)	Mn ^c (g/mol)	Mw ^c (g/mol)	Mn (theoretical)	\bar{D} ^c
MBGE	91	5688	4867	8570	14200	1.76

Table 3.5 – Synthesis of PMBGE. ^a Monomer added at 2 mL.h⁻¹ and reactions performed at 50 °C, 24 h. ^b Determined by ¹H-NMR. ^c Determined by GPC analysis.

PMBGE was then reacted with **Z-2.3** in toluene at 85 °C as these conditions had been found optimal for coupling **Z-2.3** with PMAGE (as shown in Table 3.4). The conversion of PMBGE with **Z-2.3** was found to be 35%, which was marginally lower than when **Z-2.3** was coupled with PMAGE (Table 3.6). An explanation for PMAGE offering higher conversion than PMBGE may come from the macromolecular structure of PMBGE being more branched in nature due to intermolecular ketone coupling as described in Section 1.3.2. The branching arms of PMBGE may act to limit access to the polymer and result in a decreased conversion, however this has yet to be confirmed. Overall we decided to move on with our studies focusing on PMAGE as opposed to try to improve the dispersity of PMBGE.



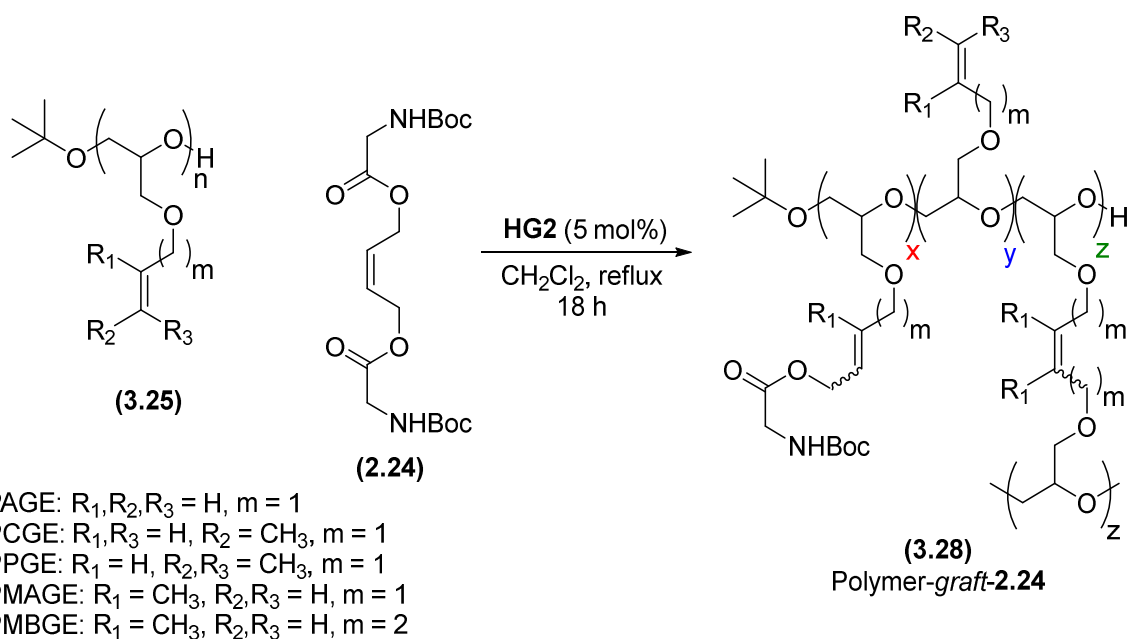
Scheme 3.11 - CM of PMBGE with AA.

		Conversion (x) ^a	Unreacted (y) ^a	Self Metathesis (z) ^a	\bar{D} before ^b	\bar{D} after ^b	Yield (%)
Entry 1	PMAGE	50	50	0	1.15	1.09	97
Entry 2	PMBGE	35	65	0	1.76	1.54	95

Table 3.6 - CM of PMAGE and PMBGE with **Z-2.3**. ^a Determined by ¹H-NMR integration. ^b Measured by GPC.

3.3.3 CM with amino acids

We moved our attention to coupling amino acids such as **2.24** to the newly synthesised polymers. Amino acid species **2.24** was chosen as the model coupling partner since we had already shown that an allyl ester at the C-terminus was the optimal way to couple glycine to the polymers (Scheme 3.12).



Scheme 3.12 - CM of PAGE, PCGE, PPGE and PMAGE with **2.24**.

Coupling this glycine species **2.24** with the new polymer (*t*-BuO)-PAGE resulted in 30% conversion, which is identical to when **2.24** was coupled to polymer (BnO)-PAGE (entry 1, Table 3.7). This similarity in conversion was surprising, considering that in the case of both MA and **Z-2.3** there was a decrease in conversion when (*t*-BuO)-PAGE was used compared to (BnO)-PAGE. However, coupling of **2.24** with (*t*-BuO)-PAGE also resulted in retention of 7% of allyl handles, compared to 0% when (BnO)-PAGE was used. This further indication that the higher molecular weight (*t*-BuO)-PAGE has an increased tendency to form hyper cross linked polymers which shield the unreacted olefins in their core.

Coupling of **2.24** with PCGE resulted in an increase in conversion to 40% (entry 2), however significant self metathesis was still prevalent. Coupling to PPGE yielded similar conversion of 38% with 27% unreacted prenyl handles remaining (entry 3). Retention of 27% of prenyl groups may also be evidence of hyper cross linked structures with the unreacted prenyl handles being held within. CM with PMAGE resulted in conversion of 30%, with no evidence of self metathesis. Once again, switching to PMBGE resulted in a surprising decrease in conversion to 24%, which may be due to branched nature of the polymer preventing adequate access for amino acid **2.24**.

		Conversion (x) ^a	Unreacted (y) ^a	Self Metathesis (z) ^a	Đ before ^b	Đ after ^b	Yield (%)
Entry 1	PAGE	30	7	63	1.16	1.81	94
Entry 2	PCGE	40	7	53	1.25	1.72	82
Entry 3	PPGE	38	27	35	1.38	1.84	95
Entry 4	PMAGE	30	70	0	1.15	1.09	97
Entry 5	PMBGE	24	76	0	1.76	1.50	90

Table 3.7 - CM of polymer range with amino acid **2.24**. ^a Determined by ¹H-NMR integration. x,y,z relate to Scheme 3.12. ^b Measured by GPC.

Since PMAGE offered the most promising results in terms of conversion vs self metathesis, we were eager to investigate how solvent choice and temperature may influence the conversion with amino acid **2.24** (Table 3.8).

Substituting CH₂Cl₂ for 1,2-dichloroethane resulted in a decrease in conversion from 30% to 25% (entry 1 and 2). Crucially, use of toluene (which had proved optimal in the coupling PMAGE with **Z-2.3**) prevented full dissolution of amino acid **2.24** but surprisingly we still observed 24% conversion (entry 3). Little improvement was observed upon increasing the temperature to 85 °C (entry 4-5), however upon increasing the temperature to 110 °C in toluene a conversion of 33% was obtained. Overall, little improvement in the conversion has been achieved from the initial reaction conditions, which means that the polymer may be limited by steric hindrance around the backbone. Importantly though, no self metathesis was observed in any of the reactions involving PMAGE.

Entry	Solvent	Temperature (°C)	Conversion ^b	Yield
1	CH ₂ Cl ₂	45	30	98
2	C ₂ H ₄ Cl ₂	45	25	94
3	Toluene	45	24	95
4	C ₂ H ₄ Cl ₂	85	22	96
5	Toluene	85	29	96
6	Toluene	110	33	98

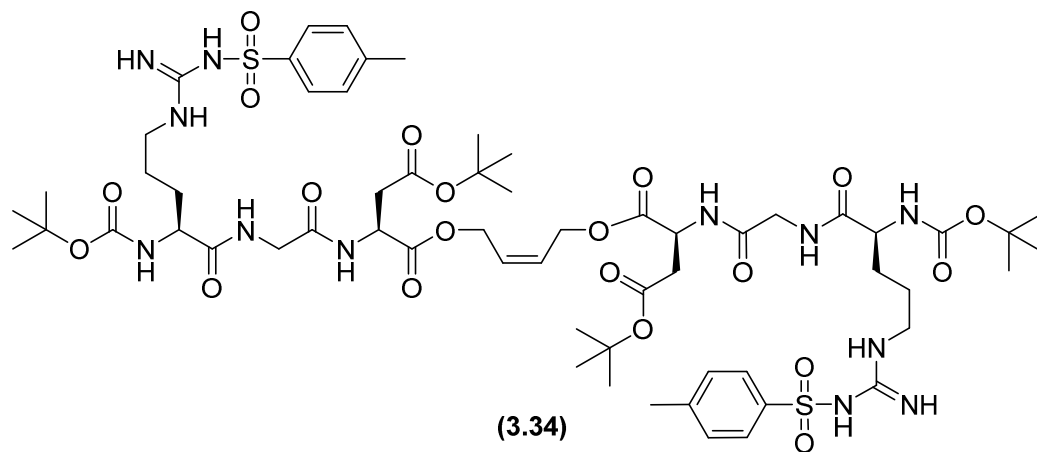
Table 3.8 - CM of PMAGE with **2.24** with various temperature and solvents ^a All reactions performed over 24 h. ^b Determined by ¹H-NMR integration.

Overall, polymers PAGE, PCGE and PPGE are able to successfully couple with glycine coupling partner **2.24** with between 30-40% conversion. This moderate conversion may be due to steric hindrance around the polymer backbone. Additionally characterisation of these products was difficult due to the high degrees of self metathesis, as this resulted in broadening of the $^1\text{H-NMR}$. Use of PMAGE and PMBGE result in slightly lower conversion of 20-30% conversion, which is likely the result of the unreactive nature of the *gem* disubstituted olefins. Due to the total absence of self metathesis of PMAGE we decided to move focus our effort on this polymer.

3.3.4 CM with RGD-O-allyl

After coupling the polymer range with a simple amino acid of glycine, we decided to attempt the coupling of PMAGE with tripeptide RGD. As described in Section 1.6, RGD is a peptide used in cell recognition, and could potentially be used to target cancerous cells by interacting with the integrin $\alpha_v\beta_3$ that is over expressed on endothelial cells that are undergoing tumour angiogenesis.^[105] We wanted to perform this coupling with PMAGE as it has been proven to prevent any self metathesis from occurring whilst offering similar conversion to the other polymers when reacted with amino acid **2.24**.

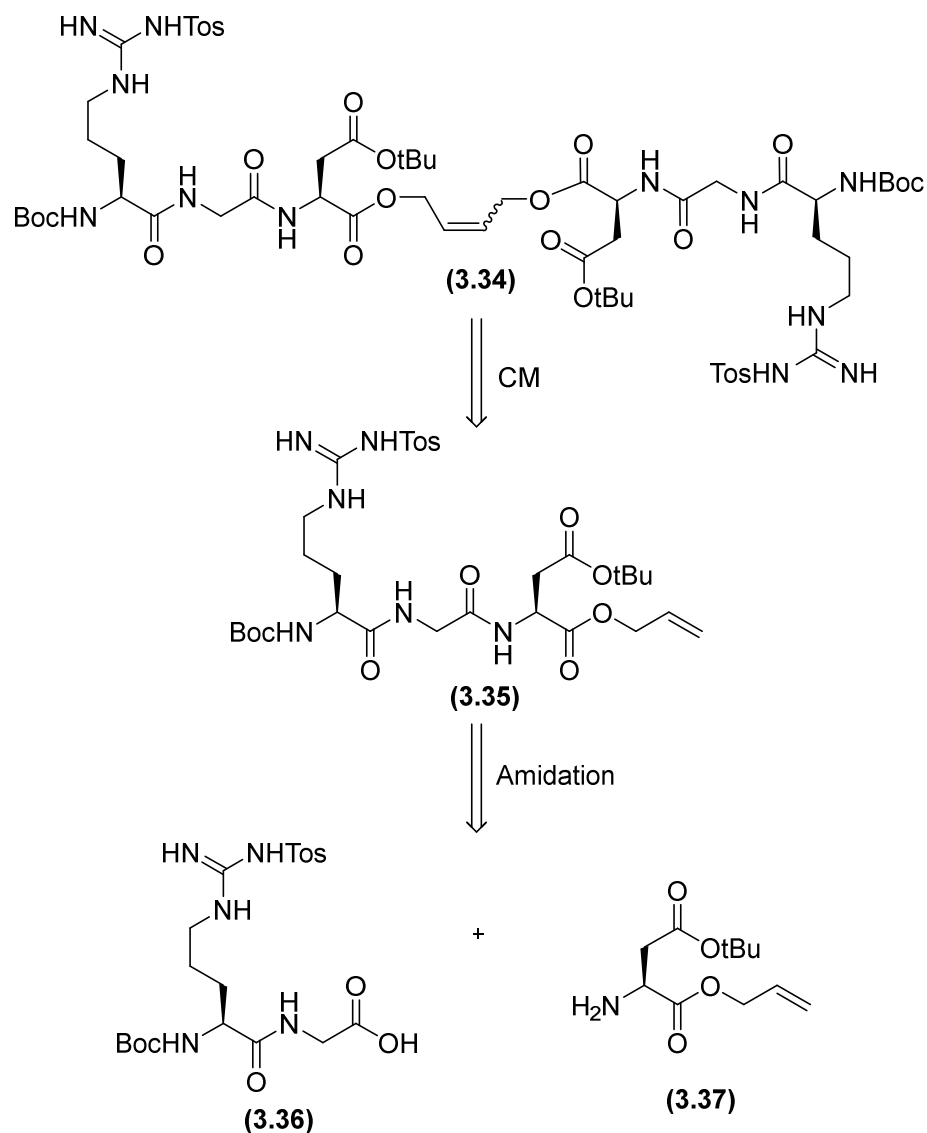
Our preliminary work on coupling peptides to polymers had found that using a pre-dimerised coupling partner with the alkene functionality installed at the C-terminus generally offered optimal conversion. For these reasons, we decided to synthesis RGD dimer **3.34**, which has an allyl ester that is analogous to **Z-2.3** and **2.24** (Scheme 3.13).



Boc-**Arg**(Tos)-**Gly**-**Asp**(tBu)-O-Butene-**Asp**(tBu)-**Gly**-**Arg**(Tos)-Boc

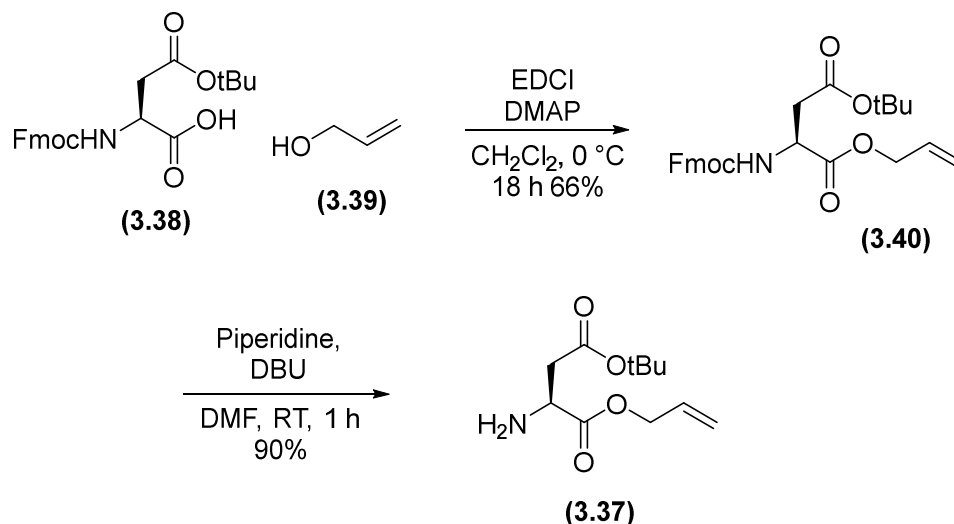
Scheme 3.13 – RGD dimer

We decided to construct RGD dimer **3.34** in a convergent synthesis by subjecting tripeptide **3.35** to cross metathesis. Tripeptide **3.5** would be synthesised by peptide coupling of dipeptide **3.36** and allyl aspartate **3.37**, which can each be made from commercially available amino acids.



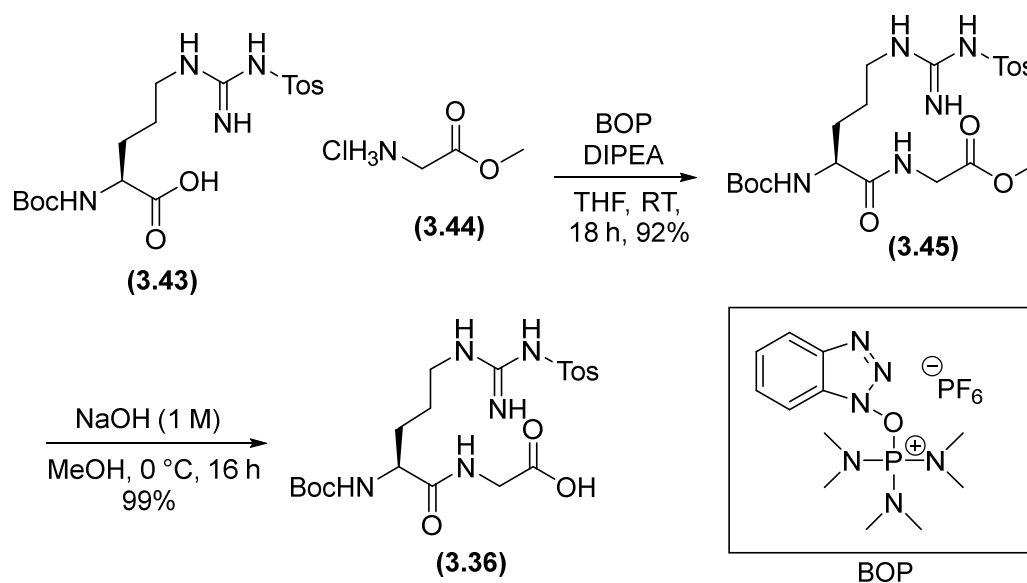
Scheme 3.14 – Retrosynthesis of RGD dimer

Synthesis of **3.37** began with the coupling of protected aspartic acid **3.38** with allyl alcohol **3.39** to form allyl ester **3.40** in 66% yield (Scheme 3.15). Subsequent removal of the Fmoc protecting group allowed the formation of the desired free amine **3.37** in 90% yield.



Scheme 3.15 – Synthesis of Asp fragment.

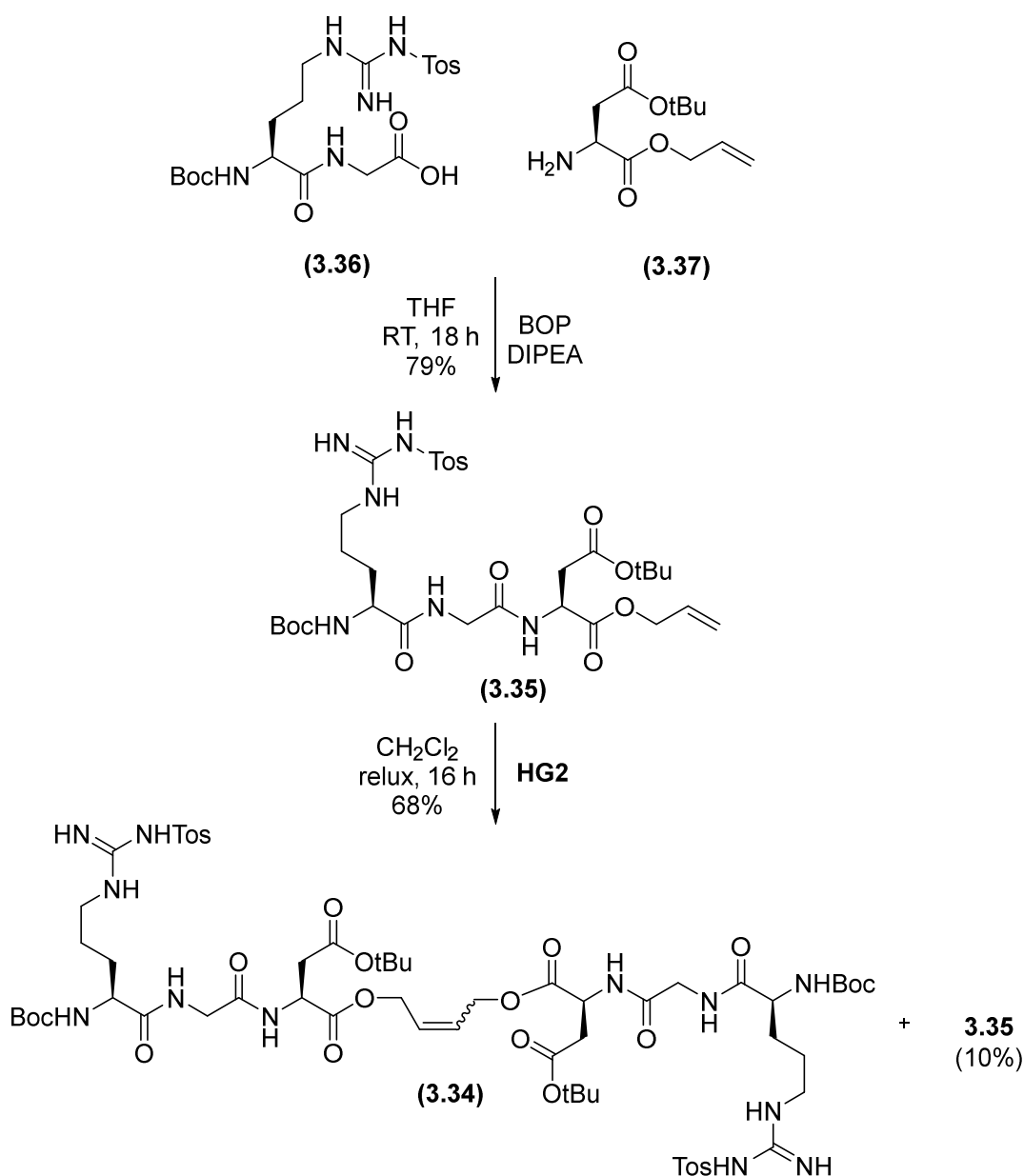
Synthesis of the Arg-Gly **3.36** fragment was done by coupling protected arginine **3.43** with methyl glycine **3.44** to furnish dipeptide **3.45** (Scheme 3.16). Hydrolysis of methyl ester **3.45** yielded the free acid **3.36** in 99% yield.



Scheme 3.16 – Synthesis of Arg-Gly dipeptide

Coupling of Arg-Gly **3.36** with aspartic acid species **3.37** using BOP allowed for the formation of RGD **3.35** in 79% yield (Scheme 3.17). Submission of **3.35** to cross metathesis conditions produced RGD dimer **3.34** in 68%, with the recovery of 10% of starting material.

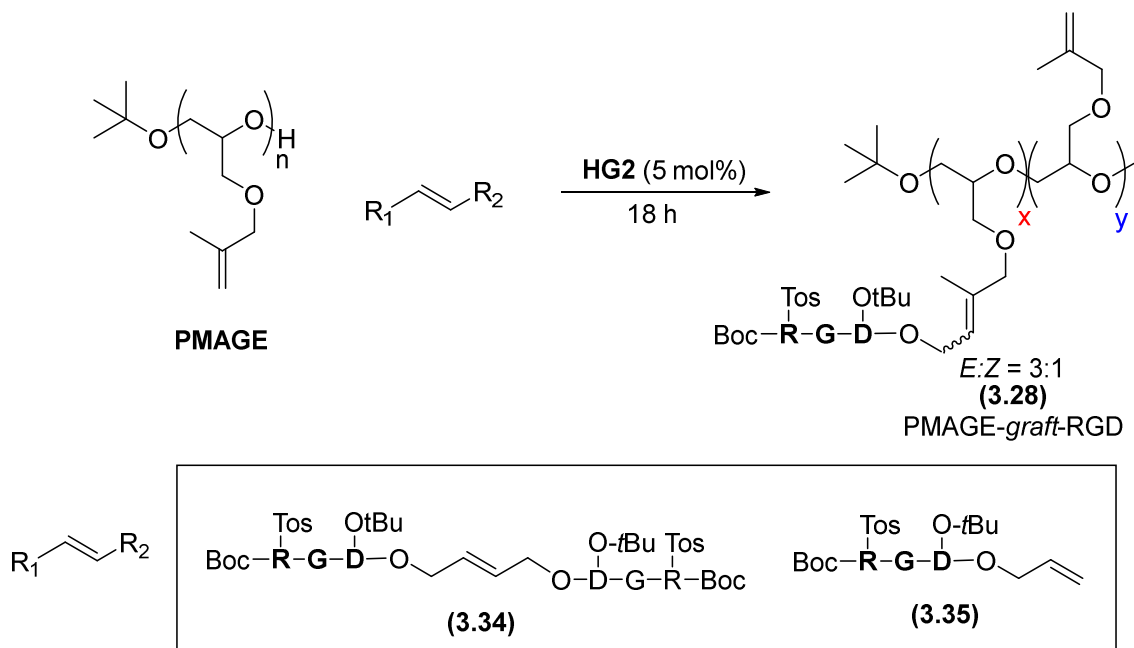
Importantly, recovery of any quantity of the allyl ester **3.35** indicated that the homodimerisation was relatively slow, and therefore both RGD **3.34** and **3.35** could be classified as a type 2 olefins.^[53]



Scheme 3.17 – RGD-O-allyl coupling

Because of the surprisingly low reactivity of the RGD-O-allyl **3.35**, it was decided to investigate the coupling of PMAGE with both RGD **3.35** and its dimer **3.34** (Scheme 3.18). Coupling of PAGE with **3.35** in CH₂Cl₂ resulted in only 5% conversion (entry 1, Table 3.9), which was expected due to the slow rate of homodimerisation of this peptide. Increasing the reaction time to 48 hours did not result in an increase in conversion, potentially indicating that the hindrance around the polymer backbone has reached its limit (entry 2). Changing the solvent to 1,2-dichloroethane did not allow for an increase in conversion (entry 3). Use

of toluene was expected to allow for a more efficient cross metathesis reaction as previously explained in section 3.3.2, however unfortunately peptide **3.35** did not dissolve in toluene. As a result, we attempted to couple RGD **3.35** in a dual solvent system of toluene/CH₂Cl₂, however this did not result in any conversion (entry 4). Use of 1,2-dichloroethane at reflux was attempted in a final effort to increase the conversion, however this resulted in only 4% conversion (entry 5). Coupling of dimer **3.34** to PMAGE did not show evidence of any conversion, which we believe is due to the hindered nature of the RGD alkene. Overall use of RGD species **3.34** and **3.35** did not prove to be efficient coupling partners with PMAGE, which we attribute to the surprisingly low reactivity of the RGD alkene.



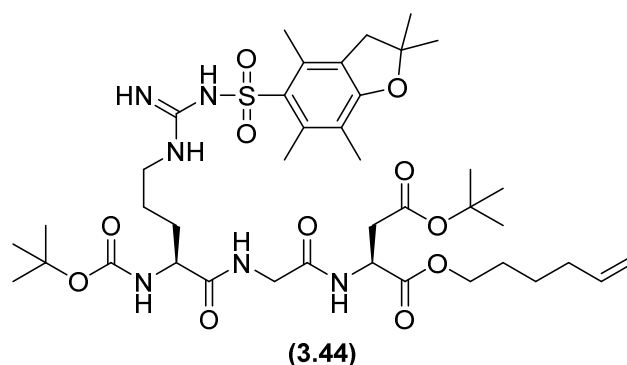
Scheme 3.18 - CM PMAGE with RGD **3.34** and **3.35**

Entry	RGD	Solvent	Temperature (°C)	Conversion ^b	Yield
1	3.35	CH ₂ Cl ₂	45	5	95
2 ^a	3.35	CH ₂ Cl ₂	45	4	86
3	3.35	C ₂ H ₄ Cl ₂	45	5	94
4	3.35	Toluene/CH ₂ Cl ₂ (1:1)	45	0	NA
5	3.35	C ₂ H ₄ Cl ₂	85	4	87
6	3.34	CH ₂ Cl ₂	45	0	NA

Table 3.9 - CM of PMAGE with RGD allyl esters **3.34** and **3.35** with various temperature and solvents ^a performed over 48 h. ^b Determined by ¹H NMR integration.

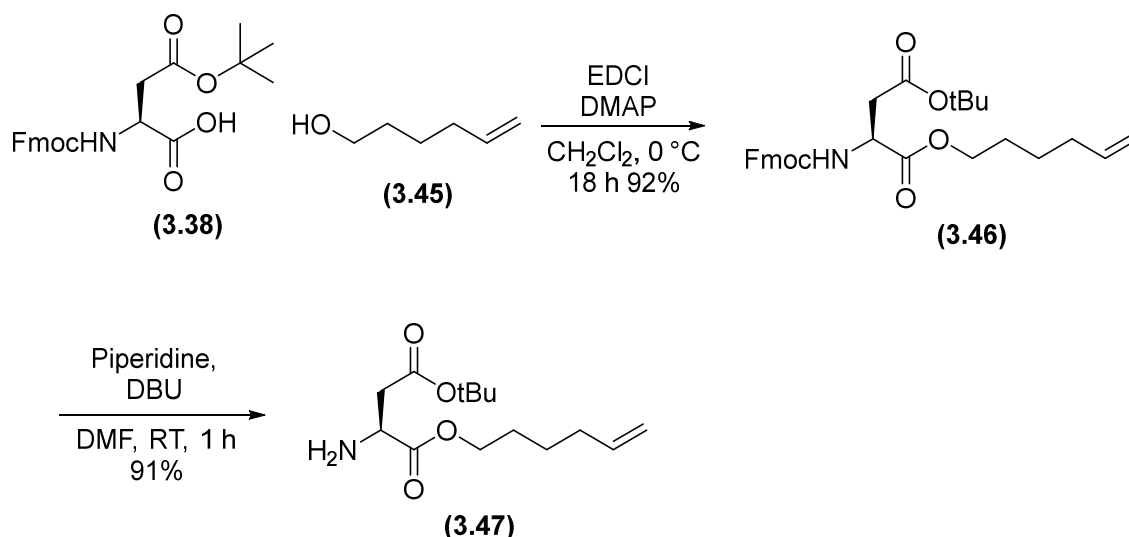
3.3.5 CM with RGD-O-hexenyl

We believe that RGD species **3.34** and **3.35** are unreactive to CM due to the close proximity of the alkene to the bulky peptide region. As a result we envisioned the use of a longer linker in order to reduce the steric hindrance around the alkene, allowing the **HG2** catalyst to access the double bond. In addition to increasing reactivity of the alkene, this linker would help prevent crowding from occurring around the polymer backbone. In order to achieve this we synthesised hexenyl ester **3.44**.



Scheme 3.19 – RGD-O-hexenyl **3.44**

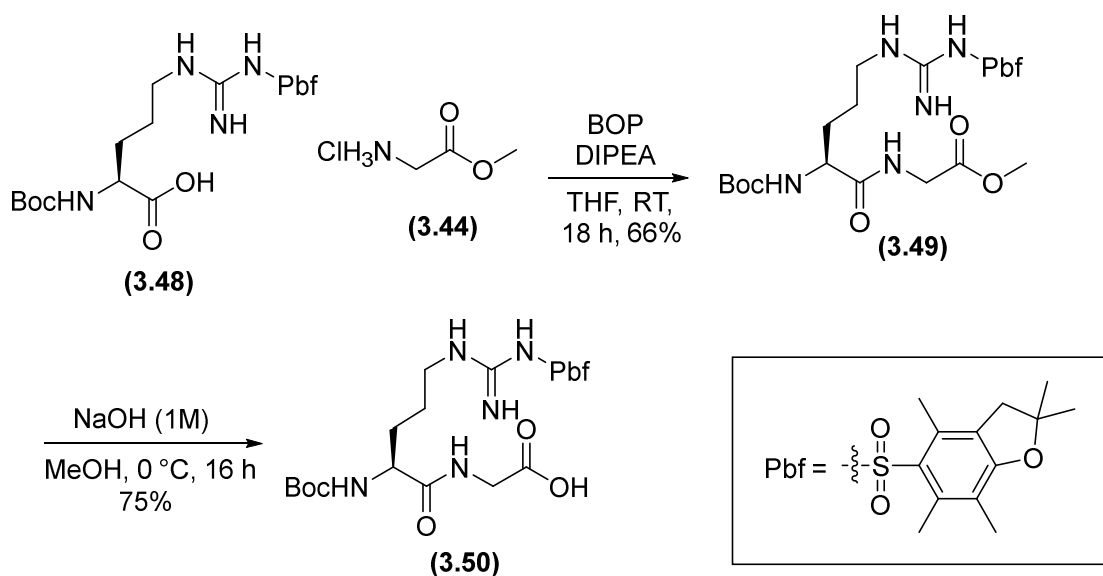
Synthesis started by coupling aspartic acid **3.38** with hex-5-ene-1-ol **3.45** to furnish ester **3.46** in 92% yield (Scheme 3.20). Deprotection of the Fmoc group formed free amine **3.47** in 91% yield.



Scheme 3.20 – Synthesis of aspartate ester.

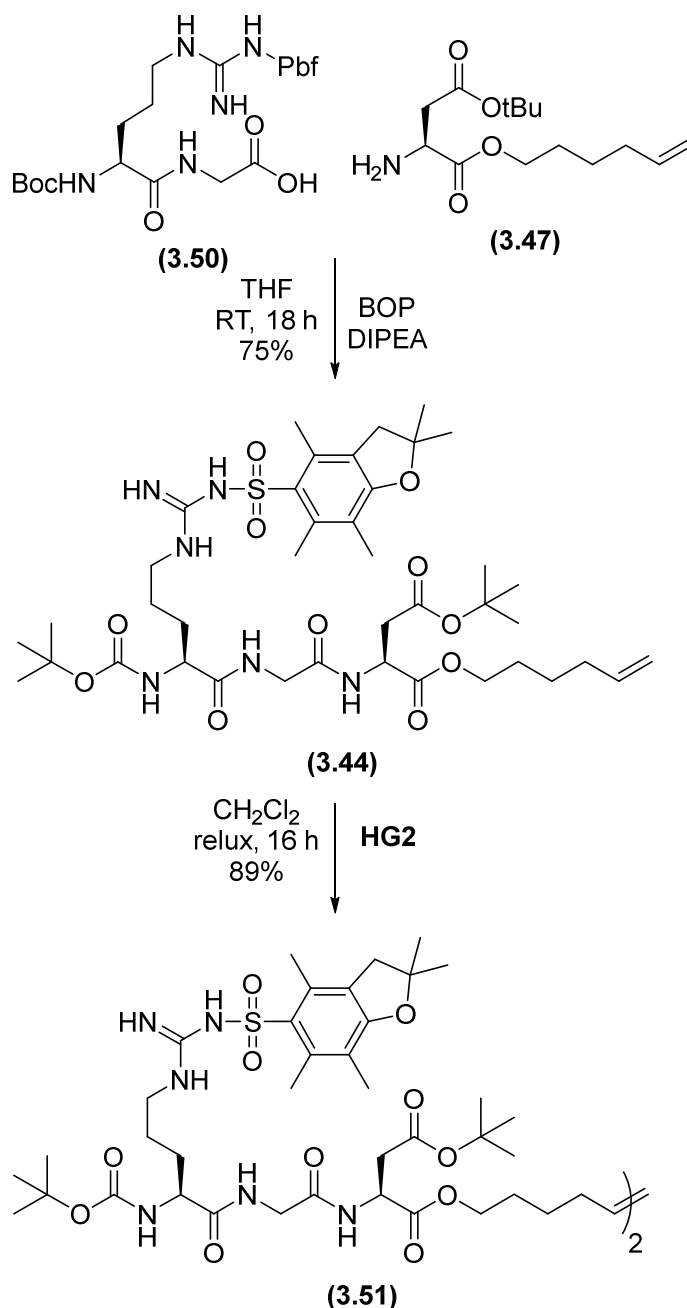
We used this repeat synthesis of RGD as an opportunity to replace the arginine's tosyl protecting group with a Pbf group, as the latter should be more easily cleaved once successfully coupled to the polymer (Scheme 3.21). Coupling of Pbf protected arginine **3.48**

with methyl glycine **3.44** yielded dipeptide **3.49** in 66% yield. In hindsight, EDCI could have been used for this coupling, which would have had the added benefit of not producing HMPA. Hydrolysis of the methyl ester then furnished fragment **3.50** in 75% yield.



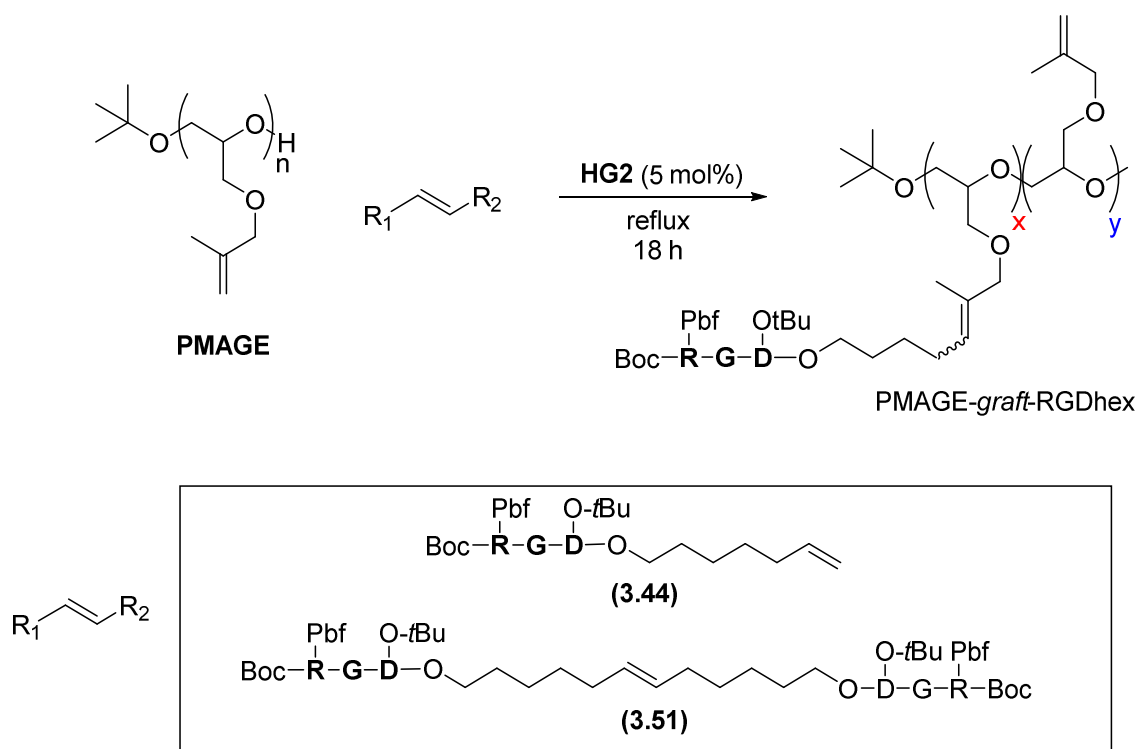
Scheme 3.21 – Synthesis of Arg(Pbf)-Gly dipeptide

Coupling of dipeptide **3.50** with hexenyl ester **3.47** resulted in the formation of RGD-O-hexenyl **3.44** in 75% yield. Homodimerisation of **3.44** was carried out, achieving 89% yield of **3.51**. Importantly no starting material was recovered, indicating that hexenyl species **3.44** is more adept to cross metathesis than allyl ester **3.35**.



Scheme 3.22 – Synthesis of RGD-O-hexenyl

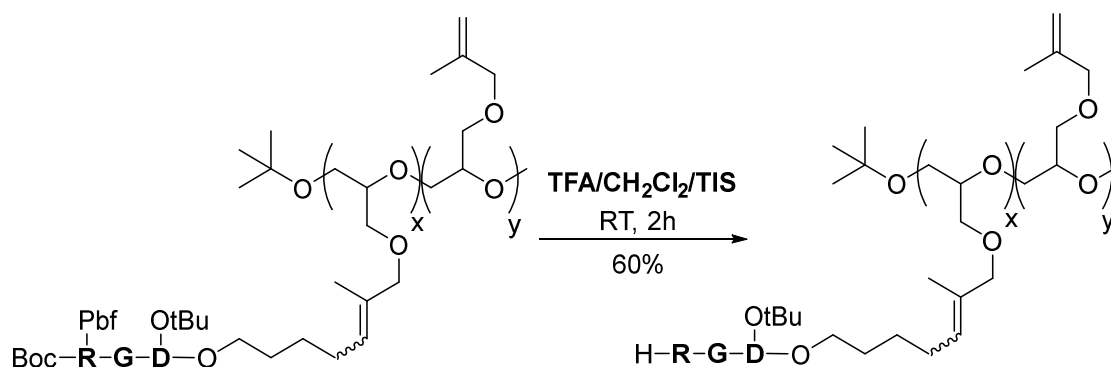
RGD-O-hexenyl **3.44** and **3.51** were then subjected to CM with PMAGE. Conjugation of **3.44** resulted in a significant increase in conversion to 31% (entry 1) compared to the CM of RGD-O-allyl **3.35**, which achieved a conversion of ~5%. Increasing the temperature to 85 °C did not result in a significant change in conversion (entry 2). Use of dimer **3.51** resulted in slightly lower conversion of 26% (entry 3). This substantial improvement in conversion is most likely due to a combination of i) increased reactivity of hexene species **3.44** and **3.51** compared to allyl esters **3.34** and **3.35**, and ii) decreased steric crowding around the polymer backbone by the large RGD molecule.



Entry	RGD	Solvent	Temperature °C	Conversion ^a	Yield (%)
1	3.44	CH ₂ Cl ₂	45	31	85
2	3.44	C ₂ H ₄ Cl ₂	85	30	90
3	3.51	CH ₂ Cl ₂	45	26	75

Table 3.10 - CM of PMAGE with RGD allyl esters **3.44** and **3.51** ^a Determined by ¹H-NMR integration.

Deprotection of the RGD conjugated polymer was then carried out using TFA. ¹H-NMR analysis of the product was not clear, however it indicated successful cleavage of the Boc and Pbf from PMAGE-*graft*-RGD, while the *tert*-butyl ester of aspartic acid appeared to remain in place. The reaction was left for 2 hours as we were concerned that cleavage of the allyl ester may occur if left for prolonged periods of time. In the future use of ZnBr₂ as a deprotection method may be worth investigating, as it has been shown to deprotect *tert*-butyl esters in the presence of allyl esters.^[111]



Scheme 3.24 – Deprotection of PMAGE-*graft*-RGD

3.4 Bifunctionalisation of copolymers PAGE-*co*-PMAGE and PPGE-*co*-PMAGE

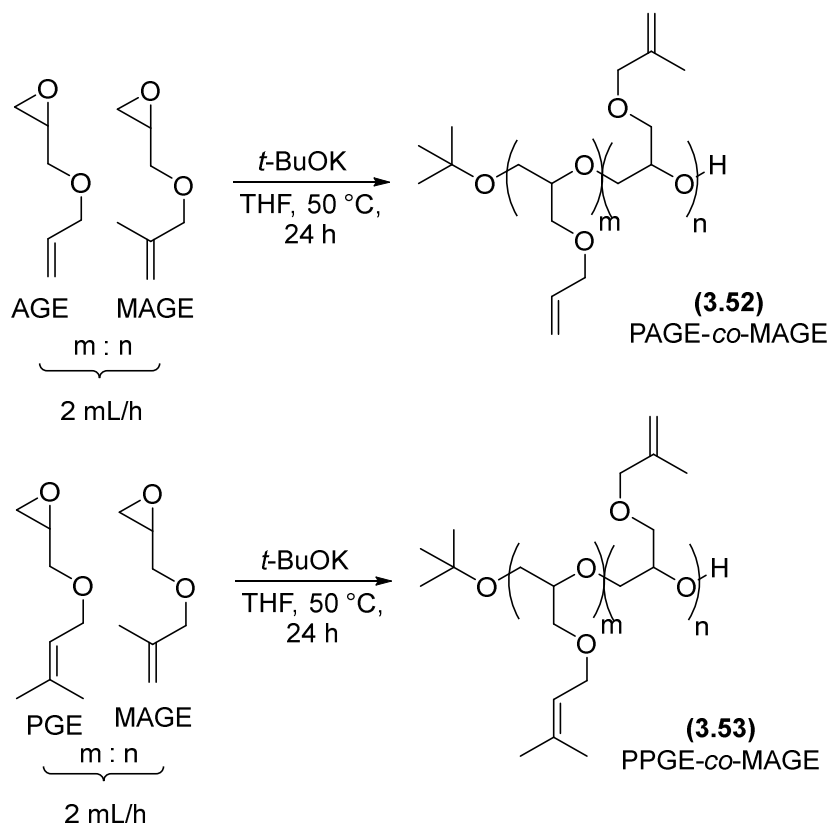
Studies on the CM of PAGE to undergo successful conjugation with methyl acrylate were promising, however GPC studies had shown evidence of self-metathesis. Therefore, it was proposed that a co-polymer of AGE and MAGE could limit the ability of self-metathesis whilst maintaining the reactivity towards CM via the remaining AGE handles. This obviously limits the ability to undergo full conversion, however it opens up the possibility to achieve bifunctionalisation if conditions can be found to utilise the difference in reactivity of AGE and MAGE. Additionally, by controlling the ratio of the two monomers during the polymerisation stage, it may be possible to dictate the ratio of polymer's bifunctionalisation. This may be extremely useful in the case of coupling both a drug and a cell targeting species to the co-polymer.

3.4.1 Co-polymer synthesis

Firstly we wanted to confirm that we could achieve bifunctionalisation by carrying out two successive CM reactions, whereby the coupling of the second partner would not result in cleavage of the first (Scheme 3.25). It was found that MA coupled polymer **3.26** was unreactive to secondary CM with type 1 coupling partner **Z-2.3**, which is due to **3.26** possessing an electron deficient, disubstituted olefin. Reversing the order of the coupling reactions so that PMAGE was conjugated with **Z-2.3** first led to polymer **3.27**, and subsequent CM with MA allowed for the displacement of allyl acetate, and formation of MA conjugated polymer **3.26**. These results indicate that, for bifunctionalisation to be achieved, it is necessary to couple the less reactive coupling partner in the first CM reaction, as this prevents displacement during the second coupling stage.



Synthesis of PPGE-co-PMAGE **3.53** was achieved with controlled ratios of x:y (entries 4-6), however at 50:50 PGE:PMAGE we observed an $M_n \sim 20$ kDa with a dispersity of 1.44, indicating that some degree of dimerisation had occurred during propagation stage (this is described in section 1.3.2).



Scheme 3.26 – Co-polymerisation of PAGE-*co*-PMAGE and PPGE-*co*-PMAGE

Entry	Monomer ^a	m:n	Mn ^b (g/mol)	Mn (theoretical)	\bar{D} ^c	Yield (%)
1	AGE:MAGE	78:22	10010	13950	1.15	99
2	AGE:MAGE	54:46	12505	13200	1.33	99
3	AGE:MAGE	24:76	7600	15670	1.38	65
4	PGE:MAGE	76:24	12480	13870	1.18	95
5	PGE:MAGE	50:50	20280	13520	1.44	91
6	PGE:MAGE	24:76	10011	13440	1.21	90

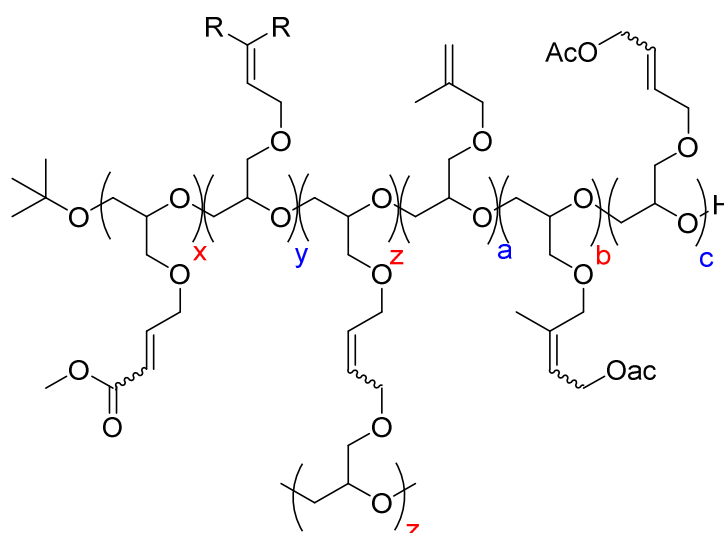
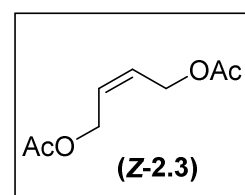
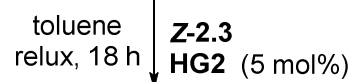
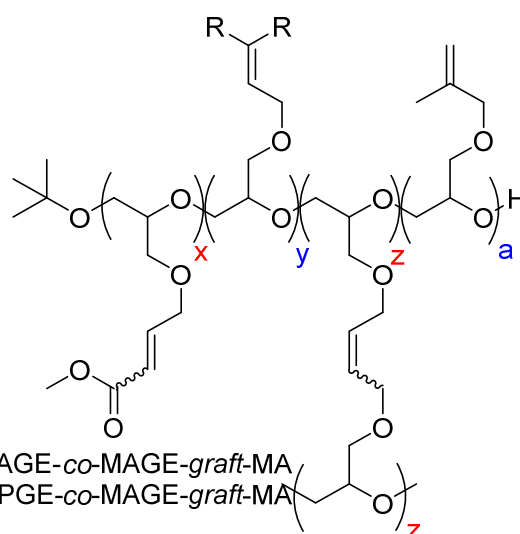
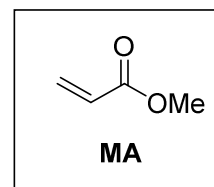
Table 3.11 - Synthesised polymer range. ^a Monomer added at 2 mL.h⁻¹ and reactions performed at 50 °C, 24 h. ^b Determined by ¹H-NMR. ^c Determined by GPC analysis.

3.4.2 CM of co-polymers

Co-polymers of PAGE-*co*-MAGE were then subjected to CM with MA, followed by **Z-2.3** (Scheme 3.27). ¹H-NMR and dispersity values were analysed after each CM reaction.

3.52: PAGE-co-PMAGE, R = H

3.53: PPGE-co-PMAGE, R = CH₃



3.54: PAGE-co-MAGE-graft-MA-graft-2.3

3.55: PPGE-co-MAGE-graft-MA-graft-2.3

Scheme 3.27 – CM of copolymers with **MA** and **Z-2.3**.

	Copolymer ratio	Starting polymer	CM with MA	Secondary CM with Z-2.3
AGE:MAGE	78:22	1.15	2.01	1.72
	54:46	1.33	1.75	1.53
	24:76	1.38	2.26	1.82
PGE:MAGE	76:24	1.18	1.91	1.65
	50:50	1.44	1.88	1.70
	24:76	1.21	1.79	1.52

Table 3.12 – Dispersity of copolymers before CM with MA, after CM with MA, after secondary CM with **Z-2.3**

		CM with MA				Secondary CM with Z-2.3				
		Polym er-MA (x)	Unreacted AGE or PGE (y)	Self metathesis (z)	MAGE (a)	Polymer- MA (x)	Unreacted AGE or PGE (y)	Self metathesis (z)	MAGE (a)	polymer- AA (b + c)
AGE: MAGE	78:22	30	8	38	24	35	0	2	26	37
	54:46	18	12	18	52	19	4	10	51	15
	24:76	8	4	7	81	17	0	3	76	3
PGE: MAGE	76:24	41	6	28	25	40	0	2	22	36
	50:50	25	9	15	51	24	3	3	44	26
	24:76	13	18	4	65	13	7	2	70	10

Table 3.13 – Conversion ratios of copolymers i) after CM with MA, and ii) after secondary CM with **Z-2.3**.

In terms of dispersity, each polymer shows an increase in dispersity after the first CM where MA is coupled to the polymer (Table 3.12, blue column). This is due to self metathesis of the polymer. Interestingly, after these polymers are subjected to the second CM reaction where **Z-2.3** is conjugated with the polymer, the dispersity values decrease in every case (Table 3.12, red column), which indicates that some of the areas of self metathesis have been converted into sites of conjugation with **Z-2.3**. This is supported by the ¹H-NMR e.g. PAGE-co-PMAGE (78:22) shows 38% self metathesis when MA is coupled, followed by 2% self metathesis when the polymer was reacted with **Z-2.3** (Table 3.13, entry 1). This ability for the homodimerised polymer to undergo coupling with **Z-2.3** is beneficial, in that it decreases the level of self metathesis (thus improving the dispersity), however this results

in **3.34/3.35** possessing both 'b' (PAGE-*graft-Z-2.3*) and 'c' (PMAGE-*graft-Z-2.3*) pendent chains (Table 3.13). This results in a complex ¹H-NMR spectrum where 'b' and 'c' are indistinguishable, and therefore the loading of **Z-2.3** onto the polymer has been categorised together as 'b+c' (Table 3.13)

In terms of successful conversion with MA, we were expecting to for ~85% of AGE handles to undergo successful conversion with MA, as this is the conversion we observed when homopolymer PAGE was coupled to MA. Surprisingly though, in all cases we observed only moderate conversion accompanied with high degrees of self metathesis. Subsequent coupling with **Z-2.3** was intended to functionalise the PMAGE areas of the copolymer, however we observed little change the percentage of PMAGE handles indicating that they had remained largely untouched. Therefore coupling partner **Z-2.3** was coupling preferentially with areas of self metathesis 'z' and areas of unreacted PAGE 'y', as indicated by the decrease in 'z' and 'y' after the second CM stage. This inability to couple **Z-2.3** with PMAGE handles may be due to the type 3 olefin being too unreactive, as well as **Z-2.3** preferentially reacting with regions 'z' and 'y'.

The bifunctionalisation of PPGE-co-PMAGE yielded similar results, however due to PGE undergoing homodimerisation slower than AGE, the degrees of self metathesis (Table 3.13) were also slightly lower than PAGE-co-PMAGE. This was also resulted in the conjugated PPGE-co-PMAGE polymers possessing a slightly lower dispersity (Table 3.12). Secondary CM with **Z-2.3** allowed for moderate conversion (Table 3.13, red column). Some of this conjugation with **Z-2.3** is due to coupling of **Z-2.3** with residual PGE and self metathesis regions, however an overall decrease in the presence of MAGE signals indicate that **Z-2.3** is, to some degree also coupling with MAGE regions.

Overall, bifunctionalisation of copolymer PAGE-co-PMAGE and PPGE-co-PMAGE has to some degree been achieved, however this conjugation with a second coupling partner has been largely due to reversible self metathesis, whereby **Z-2.3** has been coupled to the AGE or PGE region of the polymer, as opposed to the intended PMAGE handle. Future work should focus on decreasing the levels of self metathesis after the first round of CM, in order to allow the second coupling partner to couple with the MAGE handle as intended.

3.5 Conclusion

In conclusion, five new homopolymers with varying reactivities towards CM have successfully synthesised in dispersity ranging from 1.15-1.38. These polymers were then conjugated with a range of coupling partners using olefin CM. Coupling of type 2 coupling partner (MA) to the polyether was best achieved using PPGE which resulted in 95% conversion and 3% self metathesis. Unfortunately even this low degree of self metathesis resulted in an increase in dispersity from 1.38 to 2.00. With regards to type 1 coupling

partner (**Z-2.3**), PAGE resulted in the highest conversion of 87% and self metathesis of 9%, however again this was accompanied by an increase in dispersity from 1.16 to 1.46. Coupling of PMAGE with **Z-2.3** resulted in a moderate conversion of 50% using toluene at 85 °C, however most importantly this was achieved with no self metathesis and total retention of dispersity ($\mathcal{D} = 1.15$). Steric hindrance around the polymer backbone was potentially limiting the conversion of PMAGE, and so PMBGE was synthesised. Unfortunately this proved ineffective at allowing for increased conversion with coupling partners **Z-2.3**.

Coupling of amino acid **2.24** proved challenging, with all polymers limited to conversions between 24-40%. Interestingly, the in the cases of PAGE, PCGE and PPGE the absence of an extensive cross linked polymer indicated that a significant degree of self metathesis had occurred intramolecularly, potentially nanoparticle-like structures, however we have not attempted to visualize these using scanning electron microscopy (SEM). Use of PMAGE and PMBGE allow for moderate conversion with zero self metathesis, which could prove crucial in producing a monodisperse polymer-drug conjugate.

Synthesis of tripeptide RGD has been achieved with various alkene linkers being installed at the C-terminus. Coupling of these RGD species to PMAGE showed that we were able to achieve a surprisingly high conversion of 30%.

Two novel co polymers have also been synthesised; PAGE-*co*-PMAGE and PPGE-*co*-PMAGE, which allow for the bifunctionalisation of the co-polymer. Unfortunately this did not occur by the intended mechanism, e.g. whereby AGE and MAGE handles are functionalised exclusively with different coupling partners. Instead we found that the second phase of the CM resulted in the majority of the coupling partner **Z-2.3** reacting with residual AGE/PAGE handles as well as regions of self metathesis.

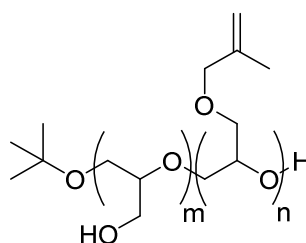
Finally, it should be noted that PEG species are commonly functionalized by end group modification, and therefore normally achieved very low loading. Our newly synthesised polymers offer a way to greatly increase the loading of drugs, with RGD coupling to PMAGE with 30% conversion.

Chapter 4 : Non-CM postpolymerisation modifications

Many of these polymers have never been synthesised before, and so we were interested to investigate how they could be functionalised using non-CM means, such as allyl ether deprotection, thiol-ene click reaction, hydroboration and dihydroxylation.

4.1.1 Allyl cleavage of copolymer

Although the use of copolymers PAGE-*co*-PMAGE and PPGE-*co*-PMAGE were restricted in terms of coupling efficiently to two different coupling partners, we were interested in using them as a possible way to improve the loading of PMAGE, which was limited to ~30-50%. We believed that this low conversion was due to steric hindrance around the polymer backbone, and so we envisaged to synthesise poly(glycidol)-*co*-(methallyl glycidyl ether), PG-*co*-PMAGE **4.1**, which has fewer MAGE handles along the polymer chain than PAGE-*co*-PMAGE or PPGE-*co*-PMAGE (Scheme 4.1). As well as inducing lower steric hindrance around the polymer backbone, the newly formed hydroxyl groups should increase the hydrophilicity of the polymer, which would be beneficial for biological systems.



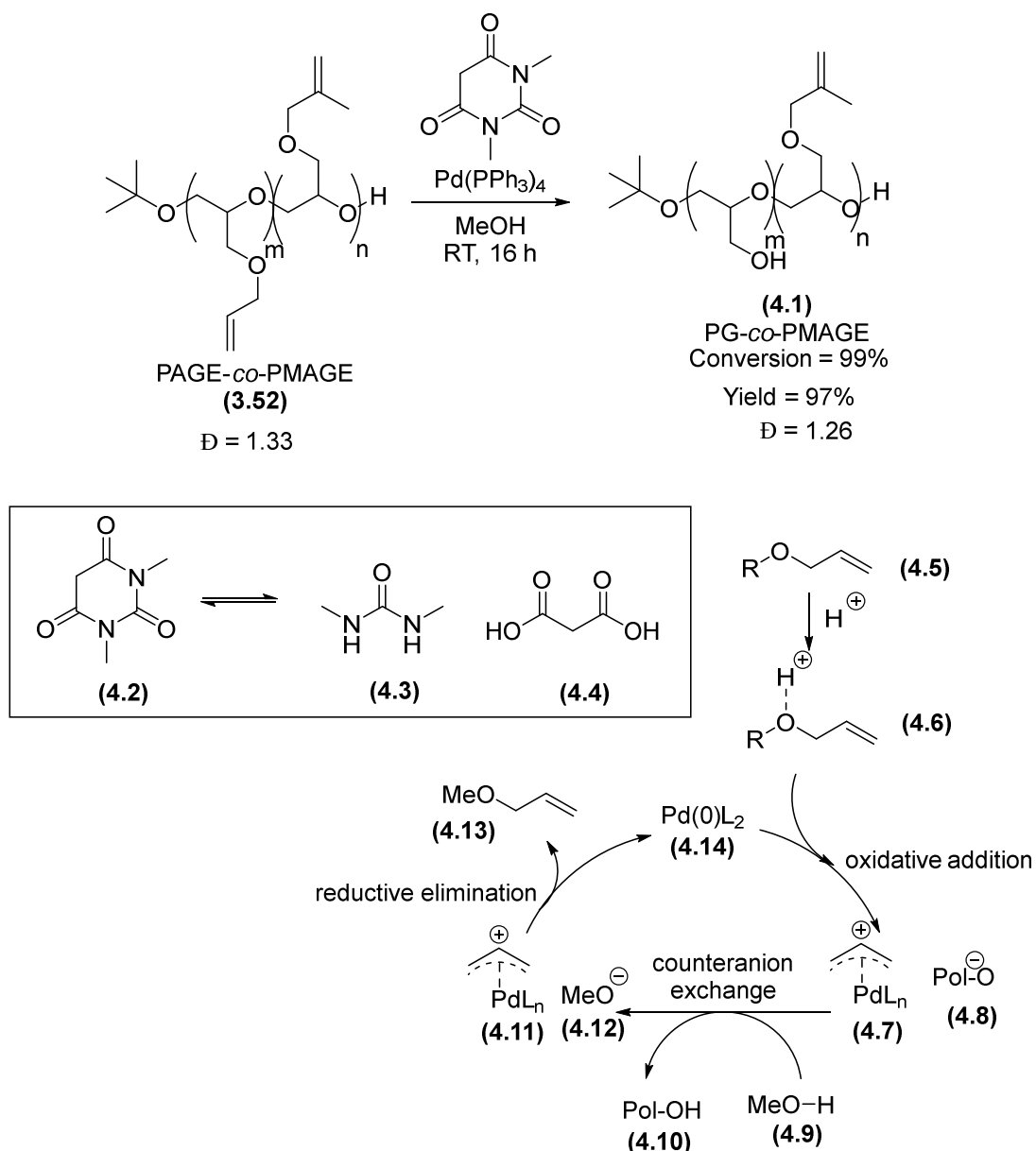
4.1
PG-*co*-PMAGE
x:y = 54:46

Scheme 4.1 – PG-*co*-PMAGE

PG-*co*-PMAGE was made from PAGE-*co*-PMAGE via Pd(0)-catalyzed deprotection of the allyl ether using barbituric acid **4.2** in methanol (Scheme 4.2).^[112] Most importantly, by controlling the reaction temperature it is possible to selectively cleave allyl, methyl allyl or prenyl ether. Using this methodology we were able to selectively cleave the allyl group of PAGE-*co*-PMAGE **3.52** to yield PG-*co*-PMAGE **4.1** in excellent yield and almost total conversion. Additionally the dispersity was found to decrease from 1.33 to 1.26. This apparent change in dispersity is likely due to a change in the coiling behaviour of PG-*co*-

PMAGE that arises from internal hydrogen bonding of the newly installed hydroxyl groups.^[38]

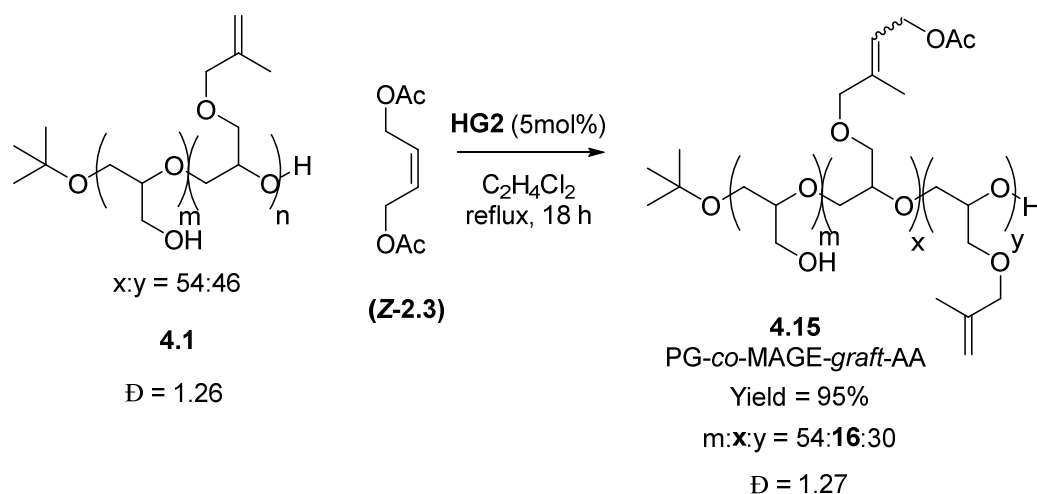
This deprotection proceeds by a typical Tsuji-Trost type mechanism, however the Brønsted acid character of **4.4** is necessary in order to activate the oxygen of ether **4.5** for oxidative addition to Pd(0) **4.14** to form η^3 -allyl complex **4.7**. Methanol is used in preference to THF for two reasons; i) the more polar solvent results in a decrease in the pKa of barbituric acid **4.2**, which is necessary for protonation of allyl ether **4.5**, and ii) it accelerates the counteranion-exchange stage.



Scheme 4.2 – Tsuji-Trost cleavage of allyl cleavage by Pd(0) as described by Kondo *et al.*^[112]

PG-co-PMAGE **5.1** was then subjected to CM with **Z-2.3** (Scheme 4.3). Due to the increased hydrophilicity of the copolymer it was not possible to use toluene as a solvent, and instead 1,2-dichloroethane was chosen. As expected, the polymer showed no evidence

of self metathesis, with a conversion of 35% of pendent methallyl handles ($x = 16\%$), which is an improvement on 23% when PMAGE was subjected to CM with **Z-2.3** under similar conditions (Section 3.3.2, Table 3.4).

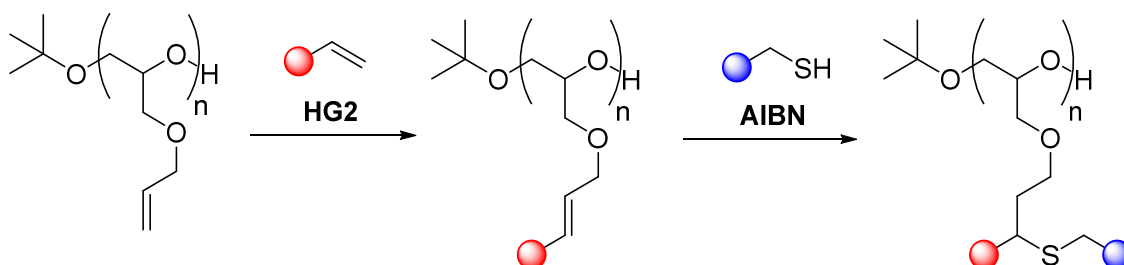


Scheme 4.3 – CM of PG-co-PMAGE with **Z-2.3**

4.1.2 Thiol-ene functionalisation of polyethers

Achieving orthogonality to functionalise co-polymers can extend beyond utilising the steric factors affecting cross-metathesis, and could be accomplished by harnessing the various olefin electronics of these novel polymers. Therefore, we wanted to investigate how thiol-ene click chemistry could be used in conjunction with cross-metathesis to achieve bi-functionalisation of the co-polymers (Scheme 4.4).

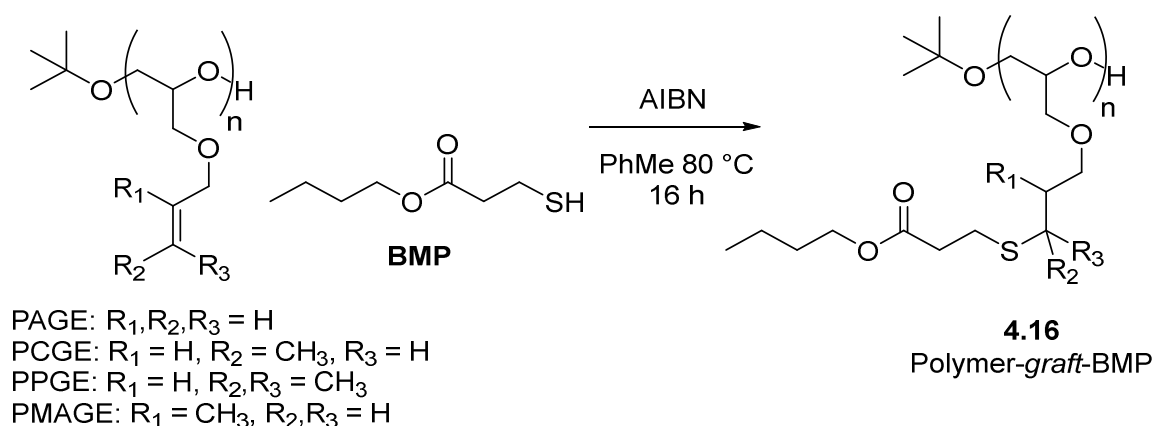
Due to the sensitivity of the CM reaction to compounds containing sulfur, it was postulated that the CM method of functionalisation should occur *before* the more robust thiol-ene click reaction. If done in the reverse order, the thiol ether on the polymer would coordinate strongly to the ruthenium centre of the **HG2** catalyst, thereby subduing the CM pathway.



Scheme 4.4 – CM on polymers followed by thiol-ene click

First we carried out the thiol-ene click reaction using AIBN initiator on non-functionalised polymers PAGE, PCGE, PPGE and PMAGE. Butyl 3-mercaptopropionate (BMP) was chosen as a coupling partner as its non-bulky structure should prevent steric hindrance around the polymer backbone (Scheme 4.5).

¹H-NMR analysis of PAGE and PMAGE coupled products indicated full conversion in good yield (Table 4.1, entry 1 and 4). However, coupling of BMP with PCGE or PPGE resulted in rapid gelation (entry 2-3).



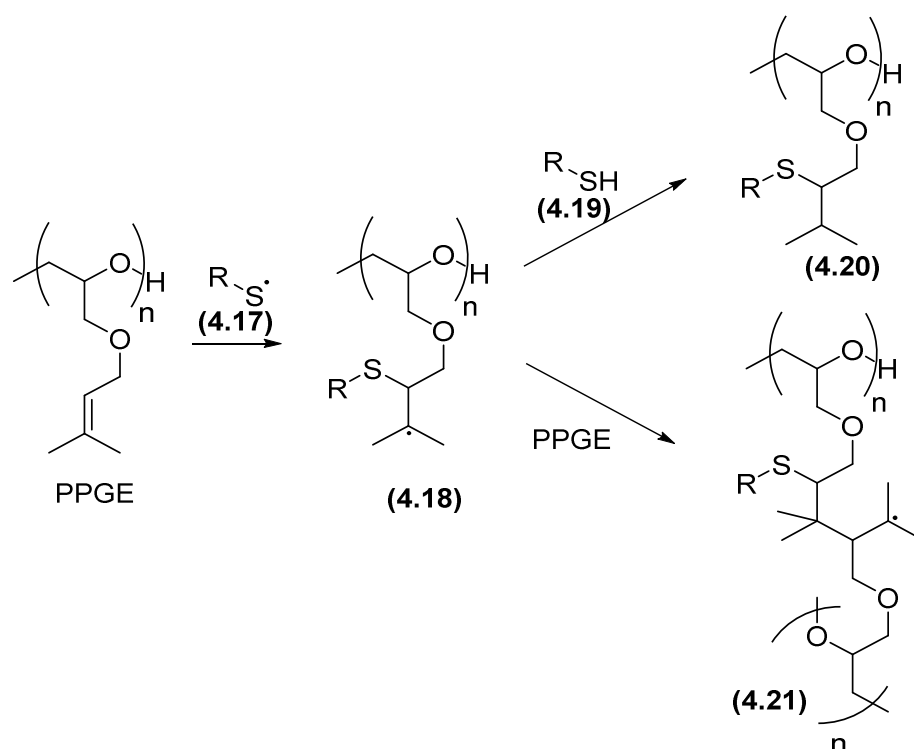
Scheme 4.5 – Thiol-ene click of BMP on PAGE, PCGE, PPGE and PMAGE

		Conversion (n) ^a	Unreacted (y) ^a	\bar{D} before	\bar{D} after	Yield (%)
Entry 1	PAGE	100	0	1.16	1.15	97
Entry 2	PCGE	Cross linking	-	1.25	-	-
Entry 3	PPGE	Cross linking	-	1.38	-	-
Entry 4	PMAGE	100	0	1.15	1.13	95

Table 4.1 - Thiol-ene of BMP on PAGE, PCGE, PPGE and PMAGE

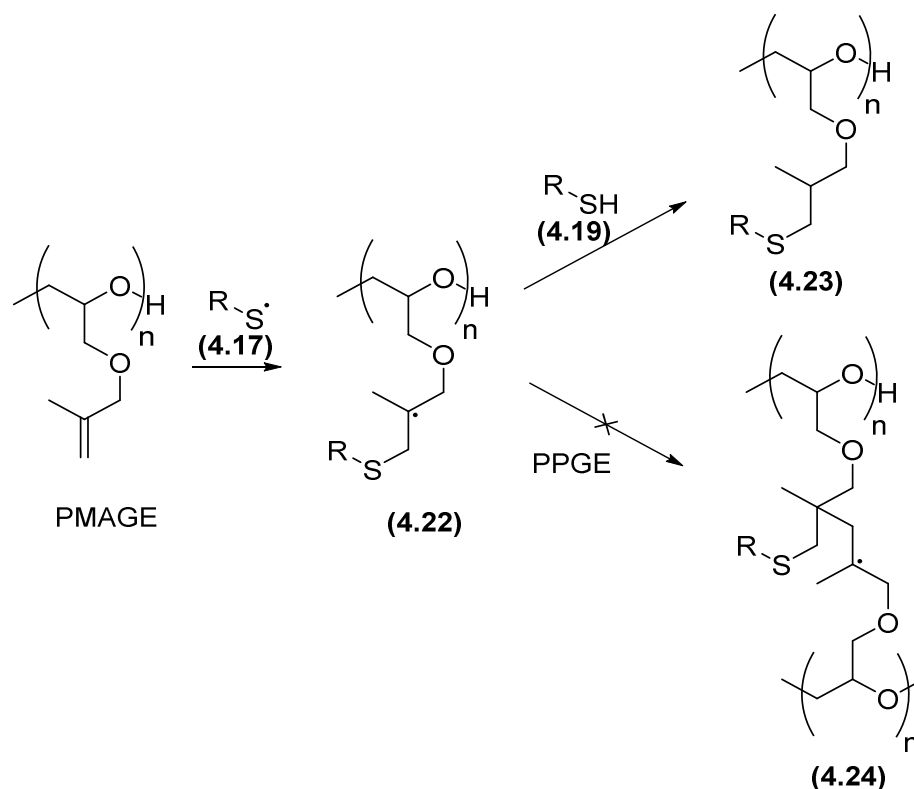
The proposed mechanism for this cross linking is as follows: thio radical **4.17** couples with the prenyl olefin of PPGE, to yield radical **4.18** (Scheme 4.6). This alkyl radical can then propagate the reaction with thiol **4.19** to yield the desired product **4.20**; however it is possible for the stabilised radical to react with another prenyl handles of a polymer chain to yield tertiary radical **4.21** (in the case of PCGE this radical would be secondary). Due to tertiary and secondary radicals being stabilised by the electron donating methyl groups, this would explain the tendency for PPGE and PCGE radical cross linking. ¹H-NMR analysis of these polymers was not possible due to their apparent network structure, therefore IR analysis employed, which indicated the presence of the thiol-ether. Such IR analysis indicates that

some degree of coupling between PPGE and BMP has taken place, however it is unquantifiable.



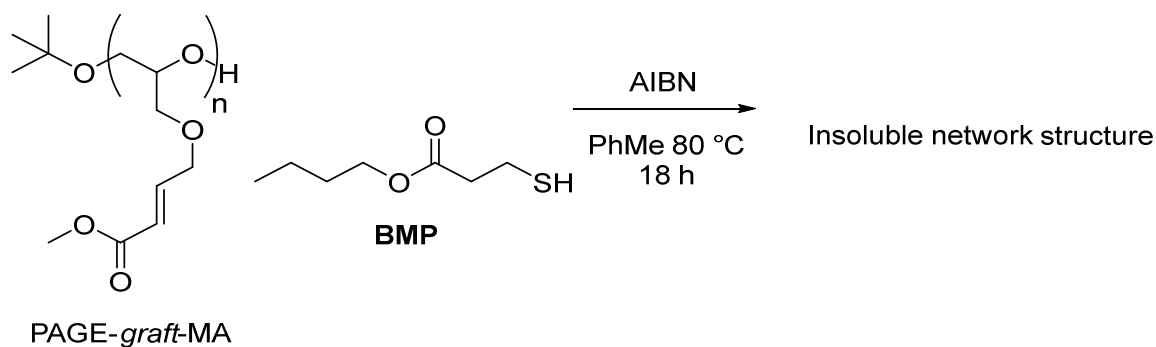
Scheme 4.6 – Cross linking mechanism of PPGE

However this reasoning does not explain why PMAGE do not undergo such cross linking, especially as PMAGE could also form a stabilised tertiary radical. We believe the reason for this is that PMAGE radical **4.22** would be located in the centre of the pendent arm (**Scheme 4.7**), and is therefore more sterically hindered than PPGE radical **4.18**, that's radical is positioned at the end of the pendent arm. This lack of accessibility means that the interstrand coupling to form **4.24** may be less likely to occur than radical propagation with thiol **4.19**.



Scheme 4.7 – Coupling of thiol with PMAGE

We then moved onto investigate the thiol-ene click reaction on a polymer that has been functionalised by CM. PAGE-*graft*-MA, that had been synthesised in section 3.3.1, was reacted with BMP using AIBN initiator, and we observed the rapid gelation of the reaction mixture (Scheme 4.8, Figure 4.1). We believe this cross linking that occurs in a similar manner to that described in Scheme 4.6, whereby PAGE-*graft*-MA is prone to radical addition by nearby polymer radicals.



Scheme 4.8 – Thiol-ene click of BMP on PMAGE-*graft*-MA

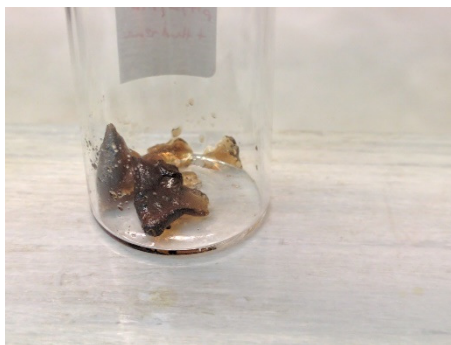


Figure 4.1 – Radically induced cross linked PAGE-graft-MA

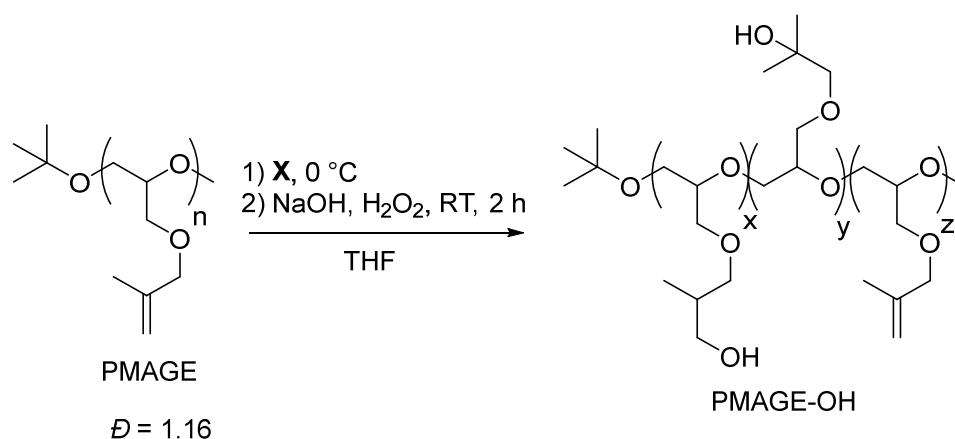
Overall, we found that PCGE and PPGE were not tolerant to thiol-ene click chemistry as they tended to form insoluble cross linked structures. PMAGE-*graft*-MA also resulted in a network structure, which we attribute to the electron deficient olefin acting as an efficient electrophile for polymer radicals. PAGE and PMAGE showed excellent reactivity with BMP as they achieved almost full conversion with no evidence of radical mediated cross linking.

4.1.3 Dihydroxylation & Hydroboration of polyethers

As discussed in Section 1.3.1 it is estimated that up to 90% of current drugs and/or drug candidates suffer from poor aqueous solubility.^[17,18] Therefore we were interested in using the olefin of the polymer to fine tune the hydrophobicity/hydrophilicity by way of hydroboration and dihydroxylation.

Hydroboration was investigated using two sources of boron; $\text{BH}_3\cdot\text{DMS}$ and 9-BBN.^[113] Unhindered $\text{BH}_3\cdot\text{DMS}$ should allow for rapid hydroboration, whereas use of 9-BBN may allow for the slower reaction, allowing for accurate tuning of the hydrophilicity by varying the reaction time.^[114] This was first conducted on PMAGE as this polymer had proved the most promising in terms of dispersity control. (**Scheme 4.9**).

As expected the use of sterically unhindered $\text{BH}_3\cdot\text{DMS}$ resulted in full conversion (**Table 4.2**, entry 1), and the regioselective synthesis of 'x' with no evidence of 'y' (**Scheme 4.9**). Sterically encumbered 9-BBN resulted in slower addition, with 55% conversion being obtained after 4 hours (entry 3). Leaving the reaction for 18 hours allowed for 80% conversion.



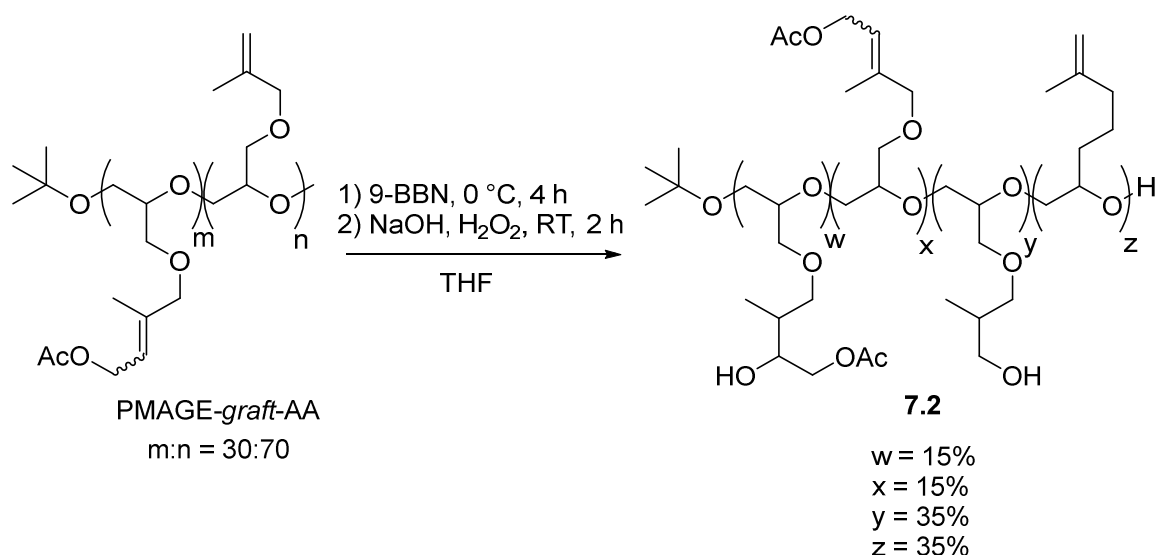
Scheme 4.9 – Hydroboration of PMAGE

Entry	X (Boron source)	Time (h)	Conversion (x) ^a	Conversion (y) ^a	Residual MAGE (z) ^a	yield	\bar{D}
1 ^b	BH ₃ . DMS	2	100	0	0	67	-
2	9-BBN	2	33	0	67	72	1.21
3	9-BBN	4	55	0	45	78	1.24
4 ^b	9-BBN	18	80	0	20	82	-

Table 4.2 – Hydroboration of PMAGE. ^a Determined by ¹H-NMR integration. x,y,z relate to **Scheme 4.9**. ^b Dispersity not measured due to polymer being insoluble in the THF (GPC continuous phase).

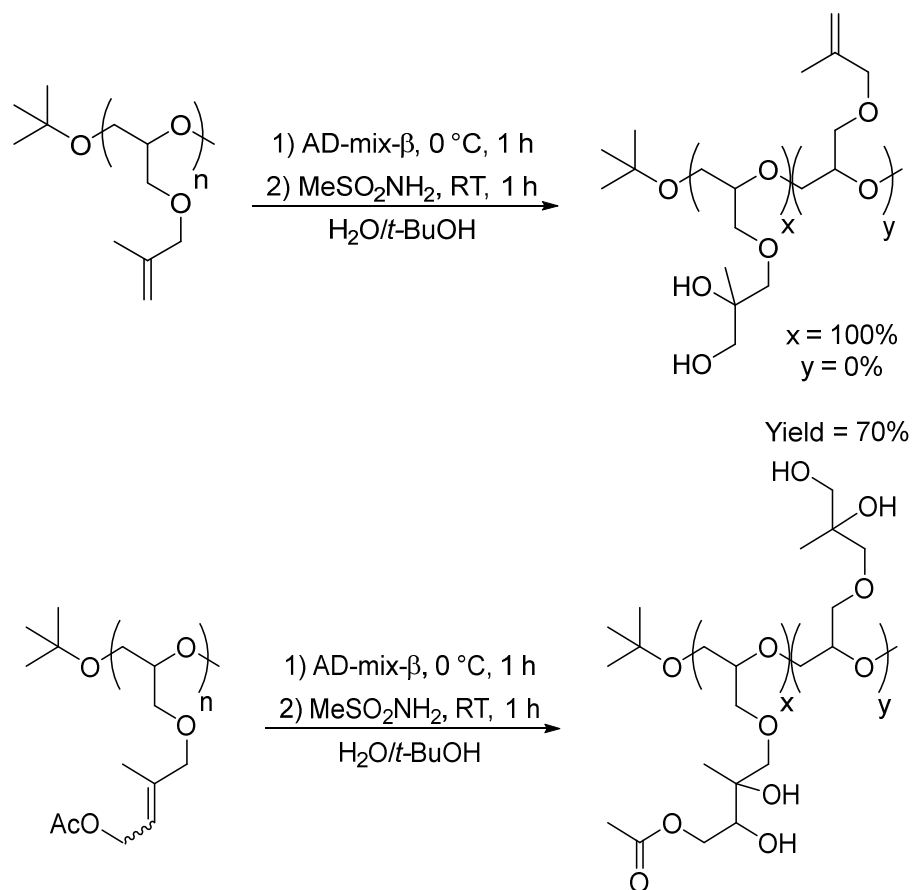
Hydroboration was also conducted on PMAGE-*graft*-AA, with the specific aim of proving that we can fine tune the degree of hydroboration of a polymer that has been functionalised by olefin CM (Scheme 4.10). Reacting 9-BBN with the polymer for 4 hours allowed 50% hydroboration to occur overall, which was composed of w = 15% and y = 35%. This degree of hydroboration is similar to that shown in Table 4.2, reinforcing the correlation between reaction time and degree of hydroboration.

As a side note, the ratio of hydroborated w:y of **7.2** is the same as the ratio of a:b in starting material PMAGE-*graft*-AA, indicating that 9-BBN does not show chemoselectivity for the functionalised handle (a) over the unreacted MAGE handle (b) (Scheme 4.10).



Scheme 4.10 – Hydroboration of PMAGE-*graft*-AA

Dihydroxylation was then carried out on PMAGE using AD-mix- β (Scheme 4.11). AD-mix was chosen in preference to OsO₄ as the former utilises fewer mol% of osmium, which would be important for pharmaceutical applications. Dihydroxylation followed by quenching with methanesulfonamide resulted in full conversion with an overall yield of 70%. Unfortunately, due to the polar nature of the resulting polymer, we were unable to analyse the polymer by GPC which uses THF as a continuous phase. Dihydroxylation was also carried out on allyl acetate functionalised polymer PMAGE-*graft*-**2.3**, which resulted in complete dihydroxylation of all alkenes present.



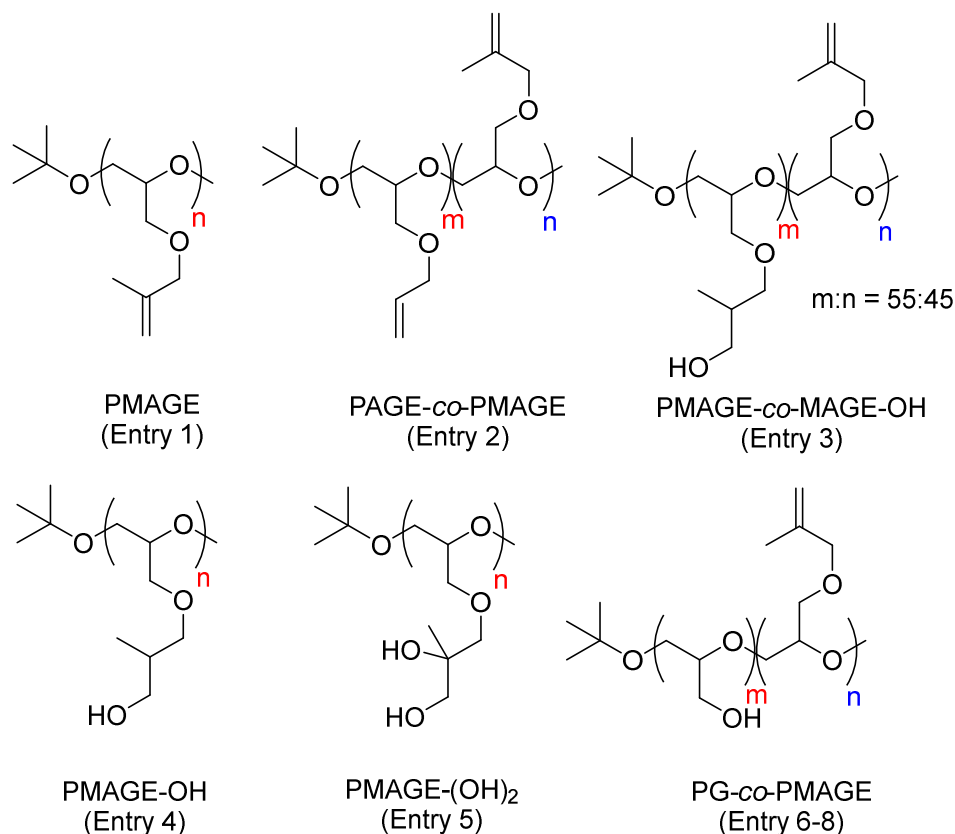
Scheme 4.11 – Dihydroxylation of PMAGE

4.1.4 Solubility testing of polyethers

With the hydroborated and dihydroxylated polymers in hand, we investigated the solubility of each polymer. Homopolymers such as PMAGE, as well as copolymer PAGE-co-PMAGE were soluble in most organic solvents however did not dissolve in more polar systems (entry 1 & 2, Scheme 4.12). PMAGE that had undergone 55% hydroboration was limited to organic solvents (entry 3), however as we moved to full conversion, the resulting polymer became soluble in only methanol and water (entry 4). As expected the full dihydroxylation of PMAGE resulted in the polymer only being soluble in polar solvents (entry 5). Copolymers of PG-co-PMAGE showed that as the ratios of m:n increased from 50:50 to 75:25, the polymer became soluble only methanol and water (entry 6-8), which demonstrates how the removal of ally group of PAGE-co-MAGE allows us to control the hydrophilicity of the polymer.

Entry	Polymer	Water	Ethanol	THF	CH ₂ Cl ₂	CHCl ₃	Toluene
1	PMAGE	×	×	✓	✓	✓	✓
2	PAGE-co-MAGE	×	×	✓	✓	✓	✓
3	PMAGE - hydroborated (55%)	×	×	✓	✓	✓	✓
4	PMAGE – hydroborated (100%)	✓	✓	×	×	×	×
5	PMAGE - Dihydroxylated (100%)	✓	✓	×	×	×	×
6	PG-co-PMAGE (25:75)	✓	✓	✓	✓	✓	×
7	PG-co-PMAGE (50:50)	✓	✓	✓	✓	✓	×
8	PG-co-PMAGE (75:25)	✓	✓	×	×	×	×

Table 4.3 - Solubility testing of various polymers. (50 mg of polymer in 1 mL of solvent.). ✓ = soluble, ✗ = insoluble



Scheme 4.12 – Range of polymers that were analysed for solubility

4.1.5 Removal of ruthenium after CM

Removal of the active ruthenium species was investigated for two main reasons; 1) to prevent self-metathesis from occurring once the reaction is over, and 2) reduce ruthenium content below the limit of 10 ppm for pharmaceutical applications.^[115,116]

We investigated three methods; size exclusion chromatography, dialysis and CupriSorb™ as possible ways of reducing the ruthenium content below our target of 10 ppm (Table 4.4). Note that column chromatography has been reported to be effective at removing ruthenium,^[117] however due to our polymers not eluting on a silica column, we were reliant on size exclusion chromatography (LH-20). Additionally due to dialysis relying on an aqueous environment, we used PG-co-PMAGE as a model compound for purification as the solubility test showed that it was water soluble.

Using only SEC we found the ruthenium content to be ~950 ppm, which was expected due to LH-20 not being selective for polarity like traditional silica chromatography. Subsequent dialysis of same crude polymer allowed for the ruthenium content to be decreased to 289 ppm. The external body of water was replaced 3 times in order to improve the outwards diffusion of the ruthenium, however in theory replacing the water even more times should

decrease the final ruthenium content further. We also experimented with CupriSorb™, which is a commercial resin designed for use in fish tanks for the removal of copper and heavy metals. Interestingly, by stirring the crude reaction mixture with this resin we were able to observe a large decrease in the ruthenium content to ~40 ppm.

Purification Method	Ru content (ppm)	%RSD ^a
Sample A – SEC (LH-20)	949.1	0.7
Sample B – subsequent dialysis*	289.1	1.3
Sample C – subsequent stirring with Cuprisorb™ **	37.8	3.5

Table 4.4 - Ruthenium content analysis. *Dialysis using SIGMA benzoylated dialysis tubing (D7884) with distilled water replacing external water three times over 48 h. ** Stirring 50 mg of polymer in 5 mL of water with 1 g of Cuprisorb™ over 48 h. ^a%RSD = percentage relative standard deviation.

4.2 Conclusion

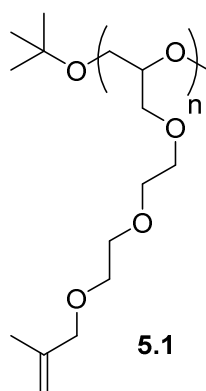
In addition to CM, we have investigated other methods of polymer modifications. A novel polymer PG-co-PMAGE was synthesised by selective cleavage of the allyl group of PAGE-co-PMAGE (synthesised in the previous chapter) using Pd(PPh₃)₄ with barbituric acid **5.2**. This reduction in the steric hindrance around the polymer backbone allowed for the successful conversion with allyl acetate species **Z-2.3** to be increased from 23% to 35% under comparative conditions.

Thiol-ene click of BMP onto the polymers was also investigated, which was successful in the cases of PAGE and PMAGE, resulting in 100% conversion. Unfortunately, coupling of BMP to PCGE, PPGE, as well as PAGE-*graft*-MA resulted in extensive cross linking, which we believe is due to the stabilised nature of the radical, allowing for facile formation of intermolecular bonding.

Use of hydroboration and dihydroxylation was conducted on the newly synthesised polymer range (PAGE, PCGE, PPGE, PMAGE, PMAGE-*graft*-AA). Employment of 9-BBN allowed use the reaction time to dictate the degree of hydroboration. This was reflected in the solubility tests, which showed that between 55% and 100% hydroboration, the polymer switched from being soluble in only organic solvents, to soluble only in more polar systems such as MeOH and water. Dihydroxylation was also carried out, which showed full conversion after 1 hour. As expected, the resulting polymer showed excellent solubility in polar solvents.

Chapter 5 : Future Work

To date, we have shown that PMAGE can be very well suited to functionalisation by olefin cross metathesis as it eliminated the possibility of self metathesis. Unfortunately, PMAGE cannot be fully functionalised, which we believe is due to steric hindrance around the polymer backbone. For this reason, we would be eager for future work to focus on the synthesis of polymer **5.1** (**Scheme 5.1**). Such a polymer would not undergo self metathesis due to the *gem*-disubstituted olefin, however the long pendent arm of the polymer should prevent crowding around the polymer backbone. This polymer would be preferable to using a linker on the coupling partner, as **5.1** would keep the site of cross metathesis away from the polymer backbone.



Scheme 5.1 – Future alternative polymer

If full conversion of polymer **5.1** can be achieved, we will move onto coupling anticancer drugs such as Taxol onto the polymer, which will allow us to investigate *in vitro* activity.

Chapter 6 : Experimental

Apparatus:

NMR spectra were recorded using a Bruker DPX-400 spectrometer (^1H NMR: 400 MHz, ^{13}C NMR: 100MHz) and a Bruker DPX-500 spectrometer (^1H NMR: 500 MHz, ^{13}C NMR: 125 MHz). Deuterated chloroform (CDCl_3) was used as the solvent for both ^1H and ^{13}C NMR, with residual solvent peak $\delta 7.27$ being used for calibration of ^1H NMR and CDCl_3 peak at $\delta 77.00$ for ^{13}C . Signal splitting patterns are described as: singlet, doublet, triplet, quartet, multiplet, broad singlet, or any combination of the above. Two dimensional experiments (COSY, HMBC, and HMQC) were recorded, where necessary, for assignment. IR spectra were recorded using a Golden Gate TM attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under FAB and CI conditions by the University of Glasgow analytical service.

Chromatography:

Flash chromatography was executed under forced flow conditions, using the indicated solvent system and the EMD Guduran silica gel 60 as solid support. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 covered aluminium sheets, and monitored by UV-light or by staining with a solution of anisaldehyde/ KMnO_4 / ninhydrin or an iodine/silica powder mixture.

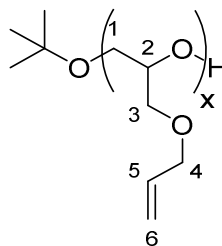
Size exclusion chromatography was executed under gravity flow conditions using Sephadex LH-20 hydroxylpropylated dextran beads with a mixed solvent of methanol: CH_2Cl_2 (1:1).

Gel permeation chromatography (GPC) was carried out using Shimadzu LPGE KIT (LC-20AT Pump, CTO-20A Oven, SPD-20A UV detector) fitted with Dr Maisch GmbH Repro-Gel GPC 1000, 5 μm column (300 \times 8 mm) at 30 $^\circ\text{C}$ with a flow rate of 1 ml/min in THF. Calibration was carried out using polystyrene standards (Polymer Labs) with M_n = 162, 3370, 60450, 915000 g/mol. Ran in unstabilised THF (VWR).

Solvents and reagents:

Reactions were collected from an in-house solvent purification system (THF, CH_2Cl_2 , Et_2O), with the exception of hexane, which was stored over 4Å MS, in a Winchester bottle. Chromatography solvents were HPLC grade solvents, stored in Winchester bottles. All reagents were used directly from supplier, unless prior purification is explicitly stated. NaH was purchased from Sigma Aldrich as 60% dispersed in mineral oil.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({allyloxy}methyl)oxirane]



PAGE

Formula: $C_4H_9O(C_6H_{10}O_2)_x$

To a 1 M solution of potassium *tert*-butoxide in THF (0.67 mL, 0.67 mmol, 1.0 equiv) was added degassed allyl glycidyl ether (7.68 g, 67.3 mmol, 100 equiv) at 2 ml/hour for 4 h. The reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomer was distilled off to afford PAGE (7.91 g, 69.3 mmol, 99%) as a yellow oil.

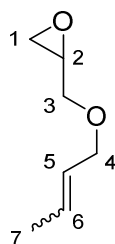
IR (ν , cm^{-1}): 2906, 2864, 1647, 1087, 920.

^1H NMR (400 MHz, CDCl_3) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3), **Section x**, 5.90 (ddt, J = 17.3, 10.0, 5.5 Hz, 1H, H^5), 5.27 (dd, J = 17.3, 1.5 Hz, 1H, $\text{H}^{6\text{trans}}$), 5.17 (dd, J = 10.4, 1.5 Hz, 1H, $\text{H}^{6\text{cis}}$), 4.00 (d, J = 5.5 Hz, 2H, H^4), 3.72–3.42 (m, 5H, H^{1-3}).

^{13}C NMR (101 MHz, CDCl_3) δ ppm: **Initiator**, not observed. **Section x**, 134.9 (C^5), 116.7 (C^6), 78.8 (C^2), 72.3 (OCH_2), 70.3 (OCH_2), 69.9 (OCH_2).

GPC: M_n = 10009, M_w = 11620, \bar{D} = 1.16.

2-((But-2-en-1-yloxy)methyl)oxirane^[118]



3.18

Formula: C₇H₁₂O₂

Molecular Weight: 128.17

To a stirring solution of NaH (11.3 g, 472 mmol, 2.00 equiv) in 500 mL of THF was added dropwise at 0 °C crotyl alcohol (*E/Z* 10/1) (34.0, 472 mmol, 1.0 equiv), and the reaction mixture allowed to stir for 30 min. To this solution was added epichlorohydrin (18.5 mL, 236 mmol, 1.00 equiv), and the reaction mixture was allowed to stir at RT for 16 h followed by 4 h at reflux.

The reaction mixture was cooled to 0 °C and quenched with water (250 mL), and THF removed under vacuum. The aqueous phase was extracted with Et₂O (3 × 250 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by distillation (bp. 110 °C at 100 mbar) followed by column chromatography (95:5, PE:Et₂O) to yield compound **3.18** as a colourless oil (18.1 g, 60%) with an *E:Z* ratio of 10:1. Data given for the *E* isomer.

IR (ν, cm⁻¹): 2978, 2862, 1657, 1450, 1111, 964.

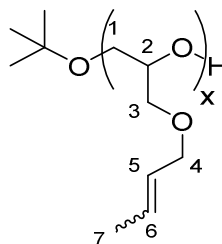
¹H NMR (400 MHz, CDCl₃) δ ppm: 5.67 (dqt, *J* = 15.3, 6.4, 1.1 Hz, 1H, H⁶), 5.51 (dtq, *J* = 15.3, 6.2, 1.6 Hz, 1H, H⁵), 3.98–3.82 (m, 2H, H⁴), 3.62 (dd, *J* = 11.4, 3.0 Hz, 1H, H^{3a}), 3.31 (dd, *J* = 11.4, 5.9 Hz, 1H, H^{3b}), 3.08 (ddt, *J* = 5.9, 4.1, 3.0 Hz, 1H, H²), 2.73 (dd, *J* = 5.0, 4.1 Hz, 1H, H^{1a}), 2.54 (dd, *J* = 5.0, 2.9 Hz, 1H, H^{1b}), 1.65 (ddt, *J* = 6.4, 1.6, 1.1 Hz, 3H, H⁷).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 130.0 (C⁵), 127.2 (C⁶), 72.0 (C⁴), 70.5 (C³), 50.8 (C²), 44.4 (C¹), 17.7 (C⁷).

HRMS (ESI) for C₇H₁₂NaO₂: 151.0735, found: 151.0743.

In agreement with literature data.^[118]

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({but-2-en-1-yl-oxy}methyl)oxirane]



PCGE

Formula: $C_4H_9O(C_7H_{12}O_2)_x$

To a 1 M solution of potassium *tert*-butoxide in THF (0.53 mL, 0.53 mmol, 1.0 equiv) was added degassed crotyl glycidyl ether **3.18** (6.86 g, 53.5 mmol, 100 equiv) at 2 ml/hour for 3.5 h. The reaction mixture was stirred at 45 °C for 20 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomer was distilled off to afford PCGE (5.80 g, 45.2 mmol, 85%) as a yellow oil.

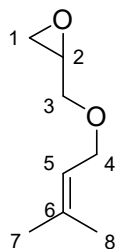
IR (ν , cm^{-1}): 2916, 2858, 1450, 1097, 964.

1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.78–5.64 (m, 1H, H^6), 5.62–5.51 (m, 1H, H^5), 3.93 (d, $J = 6.1$ Hz, 2H, H^4), 3.70–3.40 (m, 5H, H^{1-3}), 1.72 (dd, $J = 6.3, 1.0$ Hz, 3H, H^7).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 129.0 (C^5), 127.9 (C^6), 78.9 (C^2), 77.2 (C^4), 72.0, 70.1 (C^1 and C^3), 17.8 (C^7).

GPC: $M_n = 9166$, $M_w = 11443$, $\bar{D} = 1.25$.

2-(((3-Methylbut-2-en-1-yl)oxy)methyl)oxirane



3.20

Formula: C₈H₁₄O₂

Molecular Weight: 142.20

To a stirring solution of NaH (15.6 g, 649 mmol, 2.00 equiv) in 500 mL of THF was added dropwise at 0 °C prenyl alcohol (65.7 mL, 649 mmol, 2.00 equiv), and the reaction mixture allowed to stir for 30 min. To this solution was added epichlorohydrin (25.4 mL, 324 mmol, 1.00 equiv), and the reaction mixture was allowed to stir at RT for 16 h followed by 4 h at reflux.

The reaction mixture was cooled to 0 °C and quenched with water (250 mL), and THF removed under vacuum. The aqueous phase was extracted with Et₂O (3 × 250 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by distillation (bp. 110 °C at 90 mbar), followed by column chromatography (95:5, PE:Et₂O) to yield compound **3.20** as a colourless oil (25.0 g, 54%).

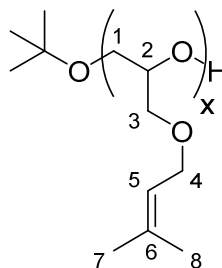
IR (ν, cm⁻¹): 2974, 2930, 2863, 1446, 1251, 1350.

¹H NMR (500 MHz, CDCl₃) δ ppm: 5.29 (t, *J* = 7.0 Hz, 1H, H⁵), 4.01–3.91 (m, 2H, H⁴), 3.62 (dd, *J* = 11.4, 3.3 Hz, 1H, H^{3a}), 3.32 (dd, *J* = 11.4, 5.8 Hz, 1H, H^{3b}), 3.19–3.15 (m, 1H, H²), 2.73 (dd, *J* = 5.0, 4.1 Hz, 1H, H^{1a}), 2.54 (dd, *J* = 5.0, 2.8 Hz, 1H, H^{1b}), 1.68 (s, 3H, H⁷ or H⁸), 1.61 (s, 3H, C⁷ or C⁸).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 137.4 (C⁶), 120.7 (C⁵), 70.7 (C³), 67.7 (C⁴), 50.9 (C²), 44.4 (C¹), 25.8 (C⁷ or C⁸), 18.0 (C⁷ or C⁸).

HRMS (ESI) for C₈H₁₄NaO₂: 165.0886, found: 165.0885

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({3-Methylbut-2-en-1-yl-oxy}methyl)oxirane]



PPGE

Formula: $C_4H_9O(C_8H_{14}O_2)_x$

To a 1 M solution of potassium *tert*-butoxide in THF (0.50 mL, 0.50 mmol, 1.0 equiv) was added degassed prenyl glycidyl ether **3.20** (7.10 g, 50.0 mmol, 100 equiv) at 2 ml/hour for 3.5 h. The reaction mixture was stirred at 45 °C for 20 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomer was distilled off to afford PPGE (6.39 g, 45.0 mmol, 90%) as a yellow oil.

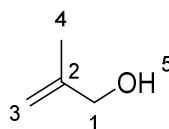
IR (ν , cm^{-1}): 2912, 2864, 1448, 1082, 983.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.34 (t, $J = 6.5$ Hz, 1H, H^5), 3.98 (d, $J = 6.5$ Hz, 2H, H^4), 3.67–3.39 (m, 5H, H^{1-3}), 1.75 (s, 3H, H^7 or 8), 1.67 (s, 3H, H^7 or 8).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 136.2 (C^6), 121.5 (C^5), 78.9* (C^2), 78.8* (C^2), 70.1, 69.9, 67.8 (C^1 & C^3 & C^4), 25.8, 18.1 (C^7 & C^8).

GPC: $M_n = 9980$, $M_w = 13778$, $D = 1.38$.

2-Methylprop-2-en-1-ol^[119]



3.22

Formula: C₄H₈O

Molecular Weight: 72.11

To a stirring solution of LiAlH₄ (25.0 g, 658 mmol, 1.00 equiv) in 1000 mL of Et₂O was added dropwise at 0 °C a solution of methyl methacrylate (70.0 ml, 658 mmol) in 200 ml of Et₂O, and the reaction mixture was allowed to stir for 1 h and warm to RT.

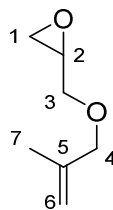
The reaction mixture was quenched with water (500 mL) at 0 °C, the aqueous phase extracted with Et₂O (3 × 500 mL), and the combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by distillation (bp. 70 °C at 100 mbar) to yield compound **3.22** as a colourless oil (34 g, 72%).

¹H NMR (500 MHz, CDCl₃) δ ppm: 4.98 (s, 1H, H^{3a}), 4.87 (s, 1H, H^{3b}), 4.05 (s, 2H, H¹), 2.22 (br s, 1H, H⁵), 1.76 (s, 3H, H⁴).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 145.0 (C²), 109.7 (C³), 66.7 (C¹), 19.1 (C⁴).

In agreement with literature data.^[119]

2-(((2-Methallyl)oxy)methyl)oxirane



3.23

Formula: C₇H₁₂O₂

Molecular Weight: 128.17

To a stirring solution of NaH (11.3 g, 472 mmol, 2.00 equiv) in 500 mL of THF was added dropwise at 0 °C 2-methyl-2-propen-1-ol (34.0 g, 472 mmol, 2.00 equiv), and the reaction mixture was allowed to stir for 30 min. To this solution was added epichlorohydrin (18.5 mL, 236 mmol, 1.00 equiv), and the reaction mixture was allowed to stir at RT for 16 h followed by 4 h at reflux.

The reaction mixture was cooled to 0 °C and quenched with water (250 mL), and THF removed under vacuum. The aqueous phase was extracted with Et₂O (3 × 250 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by distillation (bp. 100 °C at 85 mbar) followed by column chromatography (95:5, PE:Et₂O) to yield compound **3.23** as a colourless oil (24.2 g, 80%).

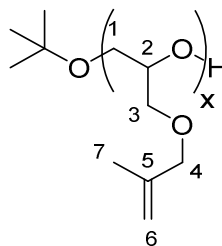
IR (ν, cm⁻¹): 2978, 2916, 2862, 1646, 1450, 1095, 902.

¹H NMR (400 MHz, CDCl₃) δ ppm: 5.01–4.98 (m, 1H, H^{6a}), 4.94–4.91 (m, 1H, H^{6b}), 3.99 (d, *J* = 12.6 Hz, 1H, H^{4a}), 3.94 (d, *J* = 12.6 Hz, 1H, H^{4b}), 3.71 (dd, *J* = 11.4, 3.1 Hz, 1H, H^{3a}), 3.40 (dd, *J* = 11.4, 5.8 Hz, 1H, H^{3b}), 3.22–3.16 (m, 1H, H²), 2.82 (dd, *J* = 5.0, 4.2 Hz, 1H, H^{1a}), 2.64 (dd, *J* = 5.0, 2.7 Hz, 1H, H^{1b}), 1.76 (s, 3H, H⁷).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 141.9 (C⁵), 112.4 (C⁶), 75.2 (C⁴), 70.5 (C³), 50.8 (C²), 44.3 (C¹), 19.4 (C⁷).

HRMS (CI) for C₇H₁₃O₂: 129.0916, found: 129.0922.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({2-Methallyl oxy}methyl)oxirane]



PMAGE

Formula: $C_4H_9O(C_7H_{12}O_2)_x$

To a 1 M solution of potassium *tert*-butoxide in THF (0.62 mL, 0.62 mmol, 1.0 equiv) was added degassed methallyl glycidyl ether **3.23** (8.00 g, 62.4 mmol, 100 equiv) at 2 mL/h for 4 h. The reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomer was distilled off to afford PMAGE (7.80 g, 60.8 mmol, 98%) as a yellow oil.

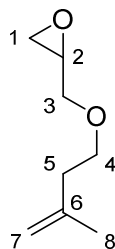
IR (ν , cm^{-1}): 2910, 2866, 1670, 1092, 897.

^1H NMR (400 MHz, CDCl_3) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3), **Section x**, 4.96 (s, 1H, H^{6a}), 4.88 (s, 1H, H^{6b}), 3.89 (s, 2H, H^4), 3.70–3.40 (m, 5H, H^{1-3}), 1.73 (s, 3H, H^7).

^{13}C NMR (101 MHz, CDCl_3) δ ppm: **Initiator**, not observed, **Section x**, 142.2 (C^5), 111.9 (C^6), 78.8 (C^2), 75.2 (C^4), 70.2, 69.9 (C^1 and C^3), 19.4 (H^7).

GPC: $M_n = 15849$, $M_w = 18239$, $\bar{D} = 1.15$.

2-(((3-Methylbut-3-en-1-yl)oxy)methyl)oxirane



3.31

Formula: C₈H₁₄O₂

Molecular Weight: 142.20

To a stirring solution of NaH (8.36 g, 348 mmol, 1.20 equiv) in 1500 mL of THF was added dropwise at 0 °C 3-methyl-3-buten-1-ol (35.3 mL, 348 mmol, 1.20 equiv), and the reaction mixture allowed to stir for 0.5 h. To this solution was added epichlorohydrin (22.8 mL, 290 mmol, 1.00 equiv), and the reaction mixture allowed to stir for 24 h at reflux.

The reaction mixture was cooled to 0 °C and quenched with water (500 mL), and THF removed under vacuum. The aqueous phase was extracted with Et₂O (3 × 250 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by distillation (bp. 120 °C at 1 mbar) followed by column chromatography (95:5, PE:Et₂O) to yield compound **3.31** as a colourless oil (18.6 g, 45%).

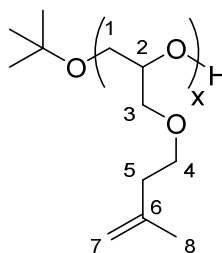
IR (v, cm⁻¹): 2865, 1652, 1456, 1375, 1253, 1107, 888, 850, 760.

¹H NMR (500 MHz, CDCl₃) δ ppm: 4.78 (s, 1H, H^{7a}), 4.73 (s, 1H, H^{7b}), 3.73 (dd, *J* = 11.6, 3.1 Hz, 1H, H^{3a}), 3.63 (dt, *J* = 9.4, 6.9 Hz, 1H, H^{4a}), 3.59 (dt, *J* = 9.4, 6.9 Hz, 1H, H^{4b}), 3.39 (dd, *J* = 11.6, 5.8 Hz, 1H, H^{3b}), 3.14 (m, 1H, H²), 2.78 (dd, *J* = 5.0, 4.1 Hz, 1H, H^{1a}), 2.60 (dd, *J* = 5.0, 2.7 Hz, 1H, H^{1b}), 2.31 (t, *J* = 6.9 Hz, 2H, H⁵), 1.74 (s, 3H, H⁸).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 142.6 (C⁶), 111.5 (C⁷), 71.5 (C³), 69.9 (C⁴), 50.8 (C²), 44.2 (C¹), 37.7 (C⁵), 22.6 (C⁸).

HRMS (ESI) for C₈H₁₄NaO₂: 165.0886, found: 165.0884.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({3-Methylbut-3-en-1-yl-oxy}methyl)oxirane]



PMBGE

Formula: $C_4H_9O(C_8H_{14}O_2)_x$

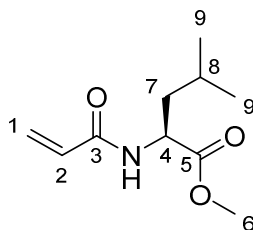
To a 1 M solution of potassium *tert*-butoxide in THF (0.6 mL, 0.60 mmol, 1.0 equiv) was added degassed methylbutenyl glycidyl ether (8.50 g, 60.0 mmol, 100 equiv) at 2 mL/hour for 4.5 h. The reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomer was distilled off to afford PMBGE (7.30 g, 51.3 mmol, 91%) as a yellow oil.

IR (ν , cm^{-1}): 2935, 2864, 1649, 1454, 1374, 1109, 886.

^1H NMR (500 MHz, CDCl_3) δ ppm: **Initiator**, 1.18 (s, 9H, CH_3), **Section x**, 4.76 (s, 1H, H^{7a}), 4.71 (s, 1H, H^{7b}), 3.65–3.40 (m, 7H, H^{1-4}), 2.29 (t, $J = 6.9$ Hz, 2H, H^5), 1.75 (s, 3H, H^8).

^{13}C NMR (126 MHz, CDCl_3) δ ppm: 142.8 (C^6), 111.4 (C^7), 78.8 (C^2), 71.0, 70.1, 70.0 (C^1 & C^3 & C^4), 37.8 (C^5), 22.8 (C^8).

GPC: $M_n = 4867$, $M_w = 8570$, $\bar{D} = 1.76$.



2.19

Formula: C₁₀H₁₇NO₃

Molecular Weight: 199.25

To a solution of *L*-Leucine methyl ester hydrochloride (2.41 g, 14.6 mmol) in 50 mL of CH₂Cl₂ was added triethylamine (2.0 mL, 15 mmol, 1.1 equiv) and acrylic acid (1.0 mL, 15 mmol, 1.1 equiv). The solution was cooled to 0 °C and DCC (3.28 g, 15.9 mmol, 1.20 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 3 h.

The reaction mixture was quenched with a 1 M aqueous solution of sodium bicarbonate (50 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and reduced under vacuum. The crude material was purified by column chromatography (7:3 PE/EtOAc) to give compound **20.19** as a colourless oil (1.40 g, 51%).

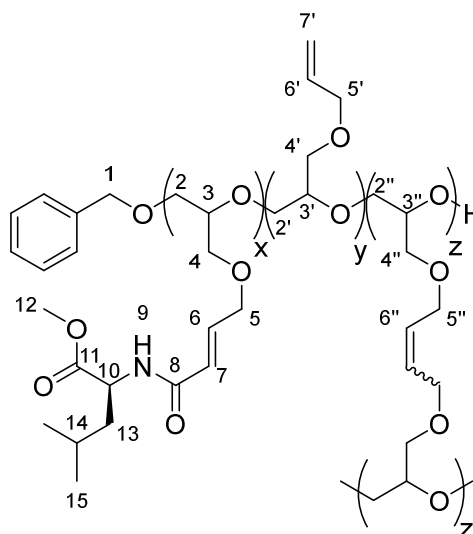
¹H NMR (500 MHz, CDCl₃) δ ppm: 6.33 (dd, *J* = 17.0, 1.4 Hz, 1H, H^{1-trans}), 6.15 (dd, *J* = 17.0, 10.3 Hz, 1H, H²), 6.05 (br d, *J* = 8.6 Hz, 1H, NH), 5.70 (dd, *J* = 10.2, 1.4 Hz, 1H, H^{1-cis}), 4.76 (dt, *J* = 8.6, 5.1 Hz, 1H, H⁴), 3.77 (s, 3H, H⁶), 1.78–1.65 (m, 2H, H⁷), 1.65–1.51 (m, 1H, H⁸), 0.98 (d, *J* = 6.2 Hz, 3H, H⁹), 0.96 (d, *J* = 6.2 Hz, 3H, H⁹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 173.8 (C⁵), 165.3 (C³), 130.4 (C²), 127.1 (C¹), 52.3 (C⁴), 50.7 (C⁶), 41.6 (C⁷), 24.9 (C⁸), 22.8 (C⁹), 21.9 (C⁹).

[α]_D²⁵ –121.5 (*c* = 1.0, CHCl₃), literature [α]_D²⁵ – unspecified.

In agreement with literature data. ^[120]

Polyether:α-oxymethylbenzene-ω-hydroxy-poly[(2*S*)-2-Acryloylamino-4-methylpentanoate-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-**2.19**

Formula: $C_7H_7O(C_{14}H_{23}NO_5)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (100 mg, 0.88 mmol, 1.0 equiv) in 2.2 mL of CH_2Cl_2 was added methyl acryloyl-*L*-leucinate **2.19** (700 mg, 3.5 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (28 mg, 0.044 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-**2.19** as a brown oil (160 mg, 83%).

IR (ν , cm^{-1}): 3318, 2956, 2928, 2912, 2872, 2249.

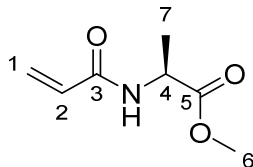
1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 7.28–7.21 (m, 5H, Ar-H), 4.62 (s, 2H, H^1), **Section x**, 7.07 (br s, 1H, H^9), 6.85 (d, $J = 16.0$ Hz, 1H, H^6), 6.25–6.15 (m, 1H, H^7), 4.69 (br s, 1H, H^{10}), 4.14 (br s, 2H, H^5), 3.80–3.45 (m, 5H, H^2 - H^4), 3.76 (s, 3H, H^{12}), 1.75–1.50 (m, 3H, H^{13} , H^{14}), 0.94 (d, $J = 4.8$ Hz, 6H, H^{15}). **Section y**, 5.90–5.75 (m, 1H, H^6), 5.27 (d, $J = 17.0$ Hz, 1H, H^{7trans}), 5.17 (d, $J = 9.4$ Hz, 1H, H^{7cis}), 4.05–3.95 (m, 2H, H^5), 3.80–3.45 (m, 5H, H^2 - H^4), **Section z**, 5.90–5.75 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.80–3.45 (m, 5H, $H^{2''}$ - $H^{4''}$). **Overall Ratio (x;y;z)** = 64:15:21 (Average Mw per unit = 220.52 g.mol $^{-1}$)

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 173.7 (C^{11}), 165.6 (C^8), 140.7 (C^6), 122.8 (C^7), 79.8* (C^3), 78.8* (C^3), 77.6, 76.6, 70.1 (C^2 & C^4 & C^5), 52.3 (C^{10}), 50.8 (CH^{12}), 41.3 (C^{13}), 24.9 (CH^{15}), 22.9 (C^{14}), **Section y**, 129.4 (C^6), 116.7 (H^7), 79.8* (C^3), 78.8* (C^3), 77.6, 76.6, 70.1 (C^2 & C^4 & C^5), **Section z**, 127.6 ($C^{6''}$), 79.8* ($C^{3''}$), 78.8* ($C^{3''}$), 77.6, 76.6, 70.1 ($C^{2''}$ & $C^{4''}$ & $C^{5''}$).

GPC: $M_n = 7580$, $M_w = 11900$, $D = 1.57$

*diastereomers

Methyl acryloyl-L-alaninate^[120]



2.20

Formula: $C_7H_{11}NO_3$

Molecular Weight: 157.17

To a solution of *L*-Alanine methyl ester hydrochloride (2.04 g, 14.6 mmol, 1.00 equiv) in 50 mL of CH_2Cl_2 was added triethylamine (2.0 mL, 15 mmol, 1.1 equiv) and acrylic acid (1.0 mL, 15 mmol, 1.1 equiv). The solution was cooled to 0 °C and DCC (3.28 g, 15.9 mmol, 1.20 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 3 h.

The reaction mixture was quenched with a 1 M aqueous solution of sodium bicarbonate (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and reduced under vacuum. The crude material was purified by column chromatography (7:3 PE/EtOAc) to give compound **2.20** as a colourless oil (1.20 g, 65%).

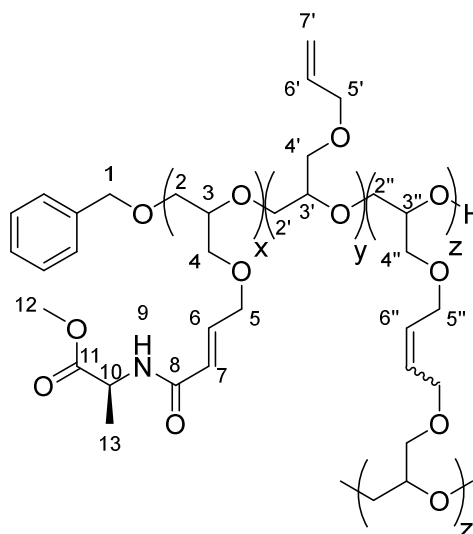
¹H NMR (500 MHz, $CDCl_3$) δ ppm: 6.31 (dd, $J = 16.9, 1.4$ Hz, 1H, $H^{1-trans}$), 6.14 (dd, $J = 16.9, 10.1$ Hz, 1H, H^2), 6.00 (br d, $J = 8.6$ Hz, 1H, NH), 5.70 (dd, $J = 10.1, 1.4$ Hz, 1H, H^{1-cis}), 4.92–4.81 (m, 1H, H^4), 3.80 (s, 3H, H^6), 1.39–1.27 (m, 3H, H^7).

¹³C NMR (126 MHz, $CDCl_3$) δ ppm: 171.1 (C^5), 162.9 (C^3), 130.3 (C^2), 126.9 (C^1), 52.5 (C^4), 51.1 (C^6), 18.9 (C^7).

$[\alpha]_D^{25}$ –155.3 ($c = 1.0$, $CHCl_3$), literature **$[\alpha]_D^{25}$** – unspecified.

In agreement with literature data. ^[120]

Polyether: α -oxymethylbenzene- ω -hydroxy-poly[(methyl (E)-4-(oxiran-2-ylmethoxy)but-2-enoyl)-L-alaninate-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-2.20

Formula: $C_7H_7O(C_{11}H_{17}NO_5)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

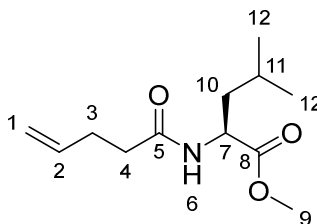
To a solution of PAGE (100 mg, 0.88 mmol, 1.0 equiv) in 2.2 mL of CH_2Cl_2 was added methyl acryloyl-L-alaninate (550 mg, 3.5 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (28 mg, 0.044 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-2.20 as a brown oil (180 mg, 81%).

IR (ν , cm^{-1}): 3320, 2970, 2930, 2903, 2820, 2310.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 7.28–7.21 (m, 5H, Ar-H), 4.62 (s, 2H, H^1), **Section x**, 7.07 (br s, 1H, H^9), 6.89 (d, $J = 16.1$ Hz, 1H, H^6), 6.23–6.12 (m, 1H, H^7), 4.69 (br s, 1H, H^{10}), 4.14 (br s, 2H, H^5), 3.82–3.45 (m, 8H, H^2 – H^4 , H^{12}), 1.35–1.25 (m, 3H, H^{13}). **Section y**, 5.88–5.75 (m, 1H, H^6), 5.27 (d, $J = 16.8$ Hz, 1H, H^{7trans}), 5.17 (d, $J = 9.3$ Hz, 1H, H^{7cis}), 4.05–3.95 (m, 2H, H^5), 3.82–3.45 (m, 5H, H^2 – H^4), **Section z**, 5.88–5.75 (m, 1H, H^6), 4.05–3.95 (m, 2H, H^5), 3.82–3.45 (m, 5H, H^2 – H^4). **Overall Ratio (x;y;z)** = 30:52:18 (Average Mw per unit = 150.25 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 172.0 (C^{11}), 165.7 (C^8), 140.7 (C^6), 128.4 (C^7), 79.9* (C^3), 78.8* (C^3), 77.8, 76.6, 70.0 (C^2 & C^4 & C^5), 53.5 (C^{10}), 52.3 (C^{12}), 22.1 (CH^{13}), **Section y**, 128.4 (C^6), 116.4 (H^7), 79.8* (C^3), 78.8* (C^3), 77.8, 76.6, 70.0 (C^2 & C^4 & C^5), **Section z**, 127.6 (C^6), 79.8* (C^3), 78.8* (C^3), 77.8, 76.6, 70.0 (C^2 & C^4 & C^5).

Methyl pent-4-enoyl-L-leucinate



2.21

Formula: C₁₂H₂₁NO₃

Molecular Weight: 227.30

To a solution of *L*-Leucine methyl ester hydrochloride (2.00 g, 11.0 mmol, 1.00 equiv) in 35 mL of CH₂Cl₂ was added triethylamine (1.60 mL, 12.1 mmol, 1.1 equiv) and 4-pentenoic acid (1.33 mL, 12.1 mmol, 1.1 equiv). The solution was cooled to 0 °C and DCC (2.43 g, 11.8 mmol, 1.2 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 3 h.

The reaction mixture was quenched with a 1 M aqueous solution of sodium bicarbonate (50 mL) and filtered. The aqueous phase was extracted with CH₂Cl₂ (3 × 25 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (65:35 PE/EtOAc) to give compound **2.21** as a colourless oil (1.70 g, 68%).

IR (ν, cm⁻¹): 3055, 2958, 1741, 1668, 1265, 732.

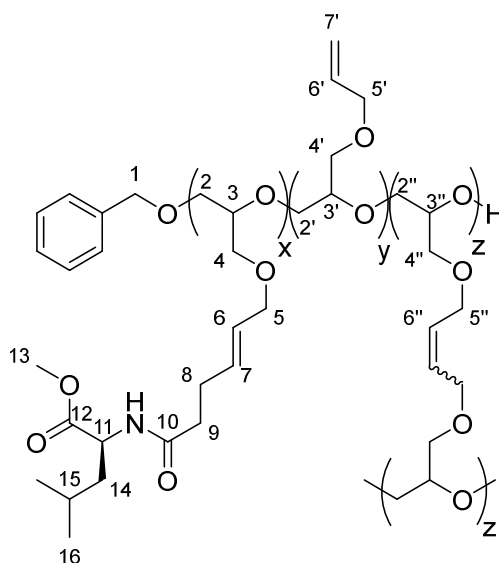
¹H NMR (400 MHz, CDCl₃) δ ppm: 5.97–5.77 (m, 2H, H² and H⁶), 5.09 (dtd, *J* = 17.1, 2.0, 1.6 Hz, 1H, H^{1-trans}), 5.03 (dtd, *J* = 10.2, 1.6, 1.2 Hz, 1H, H^{1-cis}), 4.67 (dt, *J* = 8.7, 5.0 Hz, 1H, H⁷), 3.75 (s, 3H, H⁹), 2.46–2.37 (m, 2H, H⁴), 2.37–2.29 (m, 2H, H³), 1.75–1.60 (m, 2H, H¹⁰), 1.60–1.46 (m, 1H, H¹¹), 0.98 (d, *J* = 6.2, 2.7 Hz, 6H, H¹²), 0.95 (d, *J* = 6.2, 2.7 Hz, 6H, H¹²).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 173.7 (C⁵ or C⁸), 172.0 (C⁵ or C⁸), 136.9 (C²), 115.6 (C¹), 52.2 (C⁷), 50.6 (C⁹), 41.8 (C¹⁰), 35.7 (C⁴), 29.4 (C³), 24.9 (C¹¹), 22.8 (C¹²), 22.0 (C¹²).

HRMS (ESI) for C₁₂H₂₁NNaO₃: 250.1414, found: 250.1403.

[α]_D²⁵ –165.2 (*c* = 1.0, CHCl₃).

Polyether: α -oxymethylbenzene- ω -hydroxy-poly[methyl 6-(oxiran-2-ylmethoxy)hex-4-enoyl-L-leucinate-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-2.21

Formula: $C_7H_7O(C_{16}H_{27}NO_5)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (100 mg, 0.88 mmol, 1.0 equiv) in 2.2 mL of CH_2Cl_2 was added methyl pent-4-enoyl-L-leucinate **2.21** (795 mg, 3.5 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (28 mg, 0.044 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-**2.21** as a brown oil (93.8 mg, 68%).

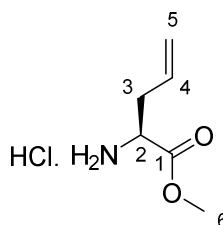
IR (ν , cm^{-1}): 3491, 3010, 2866, 2910, 2844, 1610, 1090.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 7.28–7.21 (m, 5H, Ar-H), 4.61 (s, 2H, H^1), **Section x**, 7.44 (br s, 1H, NH), 5.65–5.54 (m, 1H, H^6), 5.25–5.19 (m, 1H, H^7), 4.74 (br s, 1H, H^{11}), 4.25 (br s, 2H, H^5), 3.80–3.45 (m, 8H, H^2 – H^4 , H^{13}), 2.51–2.40 (m, 2H, H^9), 2.39–2.28 (m, 2H, H^8), 1.75–1.48 (m, 3H, H^{14} , H^{15}), 0.95 (br s, 6H, H^{16}). **Section y**, 5.85–5.74 (m, 1H, H^6'), 5.27 (br d, $J = 16.8$ Hz, 1H, $H^{7trans'}$), 5.17 (br d, $J = 9.4$ Hz, 1H, $H^{7cis'}$), 4.05–3.95 (m, 2H, H^5'), 3.80–3.45 (m, 5H, $H^{2'}$ – $H^{4'}$), **Section z**, 5.92–5.78 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.80–3.45 (m, 5H, $H^{2''}$ – $H^{4''}$). **Overall Ratio (x;y;z)** = 24:40:36 (Average Mw per unit = 156.78 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 173.7 (C^{12}), 165.6 (C^{10}), 115.4 (C^6), 110.7 (C^7), 79.5* (C^3), 78.8* (C^3), 77.6, 76.6, 70.0 (C^2 & C^4 & C^5), 51.2 (C^{11}), 50.8 (CH^{13}), 41.3 (C^{14}), 35.8 (C^8), 29.7 (C^9), 24.8 (CH^{15}), 21.4 (C^{16}), **Section y**, 128.4

(C^{6'}), 116.7 (C^{7'}), 79.5* (C^{3'}), 78.8* (C^{3'}), 77.6, 76.6, 70.0 (C^{2'} & C^{4'} & C^{5'}), **Section z**, 128.4 (C^{6''}), 79.5* (C^{3''}), 78.8* (C^{3''}), 77.6, 76.6, 70.0 (C^{2''} & C^{4''} & C^{5''}).

Methyl (S)-2-Aminopent-4-enoate.hydrogen chloride^[121]



2.13a

Formula: C₆H₁₂NO₂Cl

To a solution of allyl glycine (300 mg, 2.6 mmol, 1.0 equiv) in 6 mL of MeOH, was added freshly distilled thionyl chloride (0.25 mL, 2.9 mmol, 1.1 equiv), and the mixture was stirred at reflux for 3 h. The reaction mixture was reduced under vacuum and the product recrystallised from Et₂O, furnishing product **2.13a** as a light pink solid (399 mg, 93%).

¹H NMR (500 MHz, CDCl₃) δ ppm: 8.74 (s, 3H, NH₃), 6.10–5.64 (m, 1H, H⁴), 5.32 (d, *J* = 16.9 Hz, 1H, H^{5trans}), 5.25 (d, *J* = 10.0 Hz, 1H, H^{5cis}), 4.29 (br s, 1H, H²), 3.80 (s, 3H, H⁶), 2.90–2.82 (m, 2H, H³).

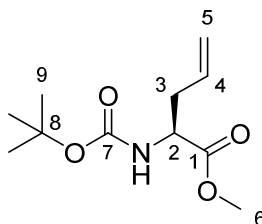
¹³C NMR (126 MHz, CDCl₃) δ ppm: 169.3 (C¹), 130.7 (C⁴), 121.2 (C⁵), 53.1 (C²), 53.0 (C⁶), 34.5 (C³).

Melting Point: 166 °C

[α]_D²⁵ +15.5 (*c* = 1.0, CHCl₃), literature **[α]_D²⁵** – unspecified.

In agreement with literature data. ^[121]

Methyl (S)-2-((*tert*-Butoxycarbonyl)amino)pent-4-enoate^[121]



2.13

Formula: C₁₁H₁₉NO₂Cl

To a solution of allyl glycine methyl ester **2.13a** (400 mg, 2.4 mmol, 1.0 equiv) in 10 mL of CH₂Cl₂, was added Boc₂O (1.05 g, 4.8 mmol, 2.0 equiv), and triethylamine (670 μ L, 4.8 mmol, 2.0 equiv), and the mixture was stirred for 24 h at RT. The reaction mixture was then diluted with H₂O (25 mL) then extracted with CH₂Cl₂ (3 \times 20 mL), the combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (70:30 PE/EtOAc) to give compound **2.13** as a clear oil (3.7 g, 70%).

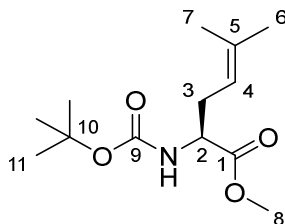
¹H NMR (500 MHz, CDCl₃) δ ppm: 5.69–5.56 (ddt, J = 17.1, 9.7, 7.2 Hz, 1H, H⁴), 5.08 (d, J = 17.1 Hz, 1H, H^{5trans}), 5.05 (d, J = 9.7 Hz, 1H, H^{5cis}), 4.98 (d, J = 6.7 Hz, 1H, NH), 4.29 (app q, J = 6.2 Hz, 1H, H²), 3.80 (s, 3H, H⁶), 2.55–2.45 (m, 1H, H^{3a}), 2.44–2.37 (m, 1H, H^{3b}), 1.37 (s, 9H, H⁹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 172.5 (C¹), 155.2 (C⁷), 132.3 (C⁴), 119.0 (C⁵), 79.9 (C⁸), 52.9 (C²), 52.2 (C⁶), 36.8 (C³), 28.3 (C⁹).

$[\alpha]_D^{25}$ +42.8 (c = 1.0, CHCl₃), literature **$[\alpha]_D^{25}$** – unspecified.

In agreement with literature data. ^[121]

Methyl (S)-2-((*tert*-Butoxycarbonyl)amino)-5-methylhex-4-enoate



2.16

Formula: C₁₃H₂₃NO₄

Molecular Weight: 257.33

To a solution of **2.13** (100 mg, 0.44 mmol, 1.0 equiv) in 5 mL of 2-methylbut-2-ene was added Grubbs' second generation catalyst (4.0 mg, 4.7 mmol, 0.01 equiv), and the mixture was stirred at reflux for 12 h. The reaction mixture was then reduced under vacuum and purified by column chromatography (9:1 PE/EtOAc) to give compound **2.16** as a colourless oil (70 mg, 73%).

IR (ν , cm⁻¹): 3445, 3360, 3349, 2976, 2955, 2931, 2861, 1746, 1717, 1501, 1437, 1393, 1366, 1354, 1275, 1248, 1207, 1165, 1111, 1059, 1024.

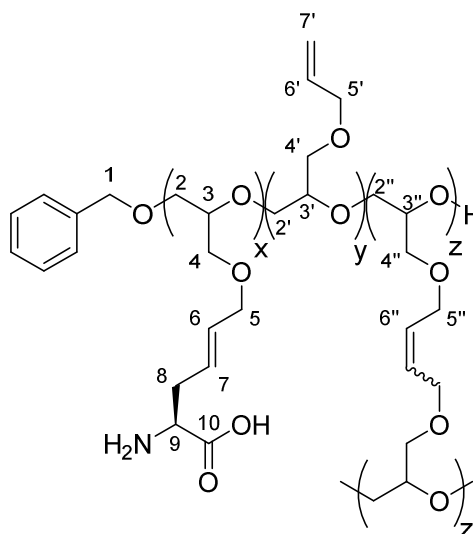
¹H NMR (500 MHz, CDCl₃) δ ppm: 5.02–4.84 (m, 2H, NH and H⁴), 4.27 (dd, J = 13.6, 5.7 Hz, 1H, H²), 3.66 (s, 3H, H⁸), 2.58–2.19 (m, 2H, H³), 1.64 (s, 3H, H⁶ or H⁷), 1.54 (s, 3H, H⁶ or H⁷), 1.37 (s, 9H, H¹¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 172.9 (C¹), 155.2 (C⁹), 136.3 (C⁵), 117.6 (C⁴), 79.8 (C¹⁰), 53.4 (C²), 52.2 (C⁸), 31.0 (C³), 28.3 (C¹¹), 25.9 (C⁶ or C⁷), 17.8 (C⁶ or C⁷).

HRMS (ESI) for C₁₃H₂₃NNaO₄: 258.1519, found: 258.1514.

$[\alpha]_D^{25}$ +6.7 (c = 1.0, CHCl₃).

Polyether: α -oxymethylbenzene- ω -hydroxy-poly[(2S)-2-amino-6-(oxiran-2-ylmethoxy)hex-4-enoic acid]-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-2.11

Formula: $C_7H_7O(C_9H_{15}NO_4)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

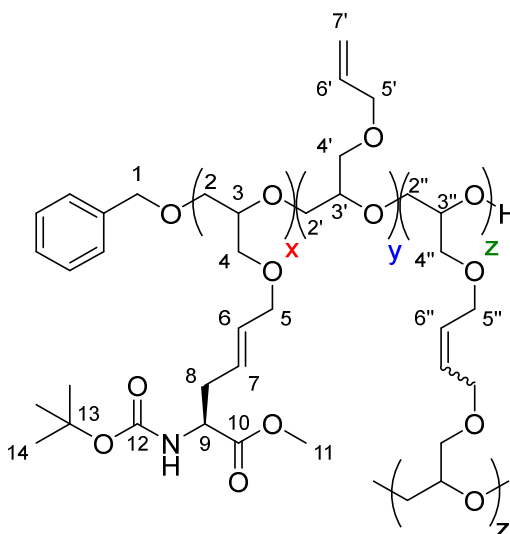
To a solution of PAGE (100 mg, 0.88 mmol, 1.0 equiv) in 2.2 mL of CH_2Cl_2 was added allyl glycine **2.11** (405 mg, 3.5 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (28 mg, 0.044 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-2.11 as a brown oil (52 mg, 50%).

IR (ν , cm^{-1}): 3475, 3410, 3010, 2771, 1635, 1115.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 7.28–7.21 (m, 5H, Ar-H), 4.61 (s, 2H, H^1), **Section x**, 7.10 (br s, 2H, NH), 5.65–5.54 (m, 1H, H^6), 5.25–5.19 (m, 1H, H^7), 4.45 (br s, 1H, H^9), 4.24 (br s, 2H, H^5), 3.88–3.39 (m, 5H, H^2 – H^4), 2.65–2.42 (m, 2H, H^8). **Section y**, 5.99–5.86 (m, 1H, $H^{6'}$), 5.31 (br d, $J = 16.9$ Hz, 1H, $H^{7trans'}$), 5.17 (br d, $J = 9.4$ Hz, 1H, $H^{7cis'}$), 4.05–3.95 (m, 2H, $H^{5'}$), 3.88–3.39 (m, 5H, $H^{2'}$ – $H^{4'}$). **Section z**, 5.99–5.86 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.88–3.39 (m, 5H, $H^{2''}$ – $H^{4''}$). **Overall Ratio (x;y;z)** = 5:90:5 (Average Mw per unit = 117.83 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 175.0 (C^{10}), 125.1 (C^6), 121.9 (C^7), 79.5* (C^3), 78.7* (C^3), 77.6, 76.1, 70.2, 68.2 (C^2 & C^4 & C^5), 50.1 (C^9), 37.2 (C^8). **Section y**, 128.3 ($C^{6'}$), 116.9 ($H^{7'}$), 79.5* ($C^{3'}$), 78.7* ($C^{3'}$), 77.6, 76.1, 70.2, 68.2 ($C^{2'}$ & $C^{4'}$ & $C^{5'}$). **Section z**, 128.4 ($C^{6''}$), 79.5* ($C^{3''}$), 78.7* ($C^{3''}$), 77.6, 76.1, 70.2, 68.2 ($C^{2''}$ & $C^{4''}$ & $C^{5''}$).

Polyether: α -oxymethylbenzene- ω -hydroxy-poly [methyl (2*S*)-2-((*tert*-butoxycarbonyl)amino)-6-(oxiran-2-ylmethoxy)hex-4-enoate]-*co*-[2-({allyl oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-2.13

Formula: $C_7H_7O(C_{15}H_{25}NO_6)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (50.0 mg, 0.44 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 was added Boc-ALG-OMe **2.13** (200 mg, 0.88 mmol, 2.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.022 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethylsulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-2.13 as a brown oil (52 mg, 68%).

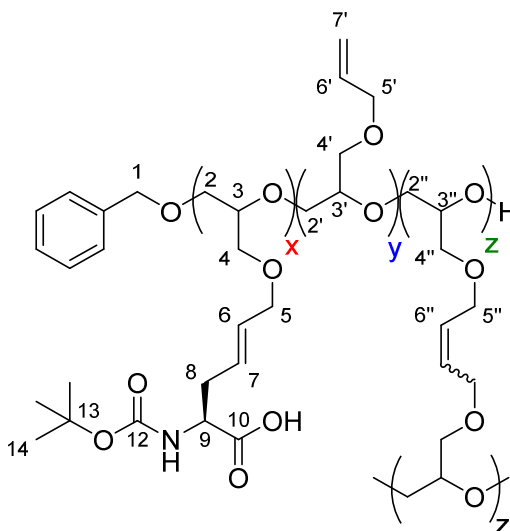
IR (ν , cm^{-1}): 2918, 2866, 1717, 1667, 1366, 1252, 1215, 1161, 1103, 1018.

1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 7.28–7.21 (m, 5H, Ar-H), 4.61 (s, 2H, H^1), **Section x**, 5.72–5.68 (m, 1H, H^6), 5.55–5.51 (m, 1H, H^7), 4.28–4.27 (m, 1H, NH), 3.91–3.90 (m, 2H, H^5), 3.86 (s, 1H, H^9), 3.77–3.02 (m, 5H, H^{2-4}), 3.67 (s, 3H, H^{11}), 2.66–2.48 (m, 1H, H^{8a}), 2.47–2.30 (m, 1H, H^{8b}), 1.37 (s, 9H, H^{14}). **Section y**, 5.97–5.85 (m, 1H, H^6), 5.31–5.27 (m, 1H, $H^{7trans'}$), 5.17–5.16 (m, 1H, $H^{7cis'}$), 4.05–3.95 (m, 2H, H^5), 3.88–3.39 (m, 5H, $H^{2'-H^4'}$), **Section z**, 5.99–5.86 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.88–3.39 (m, 5H, $H^{2''-H^4''}$). **Overall Ratio (x;y;z)** = 35:5:60 (Average Mw per unit = 176.09 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 173.1 (C^{10}), 155.3 (C^{12}), 125.2 (C^6), 121.9 (C^7), 80.2 (C^{13}), 79.4* (C^3), 78.7* (C^3), 77.5, 76.1, 70.2, 68.2 (C^2 & C^4 & C^5), 51.1 (C^9), 50.3 (C^{11}), 37.2 (C^8), 28.9 (C^{14}). **Section y**, 128.9 (C^6), 116.7 (H^7), 79.4*

(C^{3'}), 78.7* (C^{3'}), 77.5, 76.1, 70.2, 68.2 (C^{2'} & C^{4'} & C^{5'}). **Section z**, 128.4 (C^{6''}), 79.4* (C^{3''}), 78.7* (C^{3''}), 77.5, 76.1, 70.2, 68.2 (C^{2''} & C^{4''} & C^{5''}).

Polyether: α -oxymethylbenzene- ω -hydroxy-poly [(2S)-2-((*tert*-butoxycarbonyl)amino)-6-(oxiran-2-ylmethoxy)hex-4-enoic acid]-co-[2-((allyl oxy)methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PAGE-*graft*-2.12

Formula: C₇H₇O(C₁₄H₂₃NO₆)_x(C₆H₁₀O₂)_y(C₁₀H₁₆O₄)_z

To a solution of PAGE (50.0 mg, 0.44 mmol, 1.0 equiv) in 5 mL of CH₂Cl₂ was added Boc-ALG-OH **2.12** (189 mg, 0.88 mmol, 2.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.022 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethylsulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/CH₂Cl₂) furnishing PAGE-*graft*-2.12 as a brown oil (32 mg, 45%).

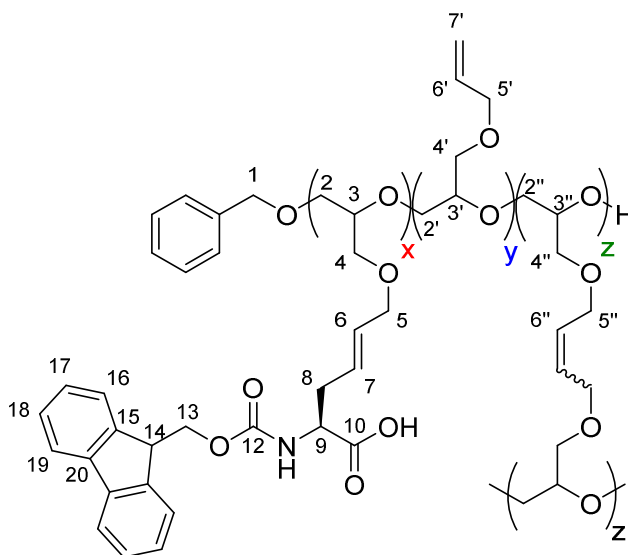
IR (v, cm⁻¹): 2918, 2711, 1748, 1621, 1252, 1211, 1161, 1018, 927.

¹H NMR (400 MHz, CDCl₃) δ ppm: **Initiator**, 7.28–7.21 (m, 5H, Ar-H), 4.61 (s, 2H, H¹), **Section x**, 5.75 (br s, 1H, H⁶), 5.60–5.52 (m, 1H, H⁷), 5.33 (s, 1H, NH), 3.91 (s, 2H, H⁵), 3.86 (s, 1H, H⁹), 3.63–3.02 (m, 5H, H²⁻⁴), 2.70–2.50 (m, 1H, H^{8a}), 2.49–2.31 (m, 1H, H^{8b}), 1.37 (s, 9H, H¹⁴). **Section y**, 5.97–5.85 (m, 1H, H^{6'}), 5.31–5.27 (m, 1H, H^{7trans'}), 5.17–5.14 (br s, 1H, H^{7cis'}), 4.05–3.92 (m, 2H, H^{5'}), 3.63–3.02 (m, 5H, H^{2'-4'}), **Section z**, 5.97–5.85 (m,

^1H , $\text{H}^{6''}$), 4.05–3.92 (m, 2H, $\text{H}^{5''}$), 3.63–3.02 (m, 5H, $\text{H}^{2''}$ – $\text{H}^{4''}$). **Overall Ratio (x;y;z)** = 30:5:65 (Average Mw per unit = 161.10 g.mol $^{-1}$).

^{13}C NMR (126 MHz, CDCl_3) δ ppm: **Initiator**, not observed. **Section x**, 171.0 (C^{10}), 155.7 (C^{12}) 125.1 (C^6), 122.3 (C^7), 81.1 (C^{13}), 79.4* (C^3), 78.7* (C^3), 77.7, 76.1, 70.2, 68.3 (C^2 & C^4 & C^5), 51.1 (C^9), 37.2 (C^8), 28.9 (C^{14}). **Section y**, 128.8 (C^6), 116.7 (H^7), 79.4* (C^3), 78.7* (C^3), 77.7, 76.1, 70.2, 68.3 ($\text{C}^{2'}$ & $\text{C}^{4'}$ & $\text{C}^{5'}$). **Section z**, 128.4 ($\text{C}^{6''}$), 79.4* ($\text{C}^{3''}$), 78.7* ($\text{C}^{3''}$), 77.7, 76.1, 70.2, 68.3 ($\text{C}^{2''}$ & $\text{C}^{4''}$ & $\text{C}^{5''}$).

Polyether: α -Oxymethylbenzene- ω -hydroxy-poly [methyl (2*S*)-2-([9-fluoren-9-yl]methoxy)carbonyl)amino]-6-(oxiran-2-ylmethoxy)hex-4-enoic acid]-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-2.14

Formula: $\text{C}_7\text{H}_7\text{O}(\text{C}_{24}\text{H}_{25}\text{NO}_6)_x(\text{C}_6\text{H}_{10}\text{O}_2)_y(\text{C}_{10}\text{H}_{16}\text{O}_4)_z$

To a solution of p(AGE) (100 mg, 0.88 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 was added Fmoc-ALG-OH (1.2 g, 3.5 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (28 mg, 0.044 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethylsulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-2.14 as a very viscous brown oil (111 mg, 74%).

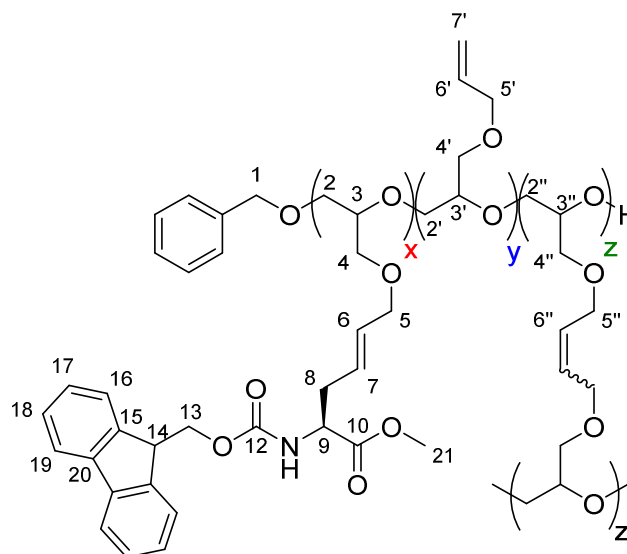
IR (ν , cm^{-1}): 3063, 3040, 3018, 2915, 2868, 2803, 1719, 1609, 1510, 1478, 1464, 1451, 1408, 1331, 1302, 1248, 1221, 1103, 1082, 1009.

^1H NMR (400 MHz, CDCl_3) δ ppm: **Initiator**, 4.61 (s, 2H, H^1), **Section x**, 7.74 (br s, 2H, Ar-H), 7.58 (br s, 2H, Ar-H), 7.46–7.15 (br m, 4H, Ar-H), 5.76–5.73 (m, 1H, H^6), 5.64–5.60 (m,

1H, H⁷), 4.52-4.98 (m, 2H, H¹³), 4.45-4.38 (m, 2H, H⁹ and H¹⁴), 4.21-4.19 (m, 2H, H⁵), 4.11-4.08 (m, 1H, NH), 3.82–2.95 (m, 5H, H²⁻⁴), 2.60 (br s, 2H, H⁸). **Section y**, 5.99-5.81 (m, 1H, H^{6'}), 5.32-5.29 (m, 1H, H^{7trans'}), 5.18-5.15 (m, 1H, H^{7cis'}), 4.05-3.92 (m, 2H, H^{5'}), 3.82–2.95 (m, 5H, H^{2'-H^{4'}}), **Section z**, 5.99-5.81 (m, 1H, H^{6''}), 4.05-3.92 (m, 2H, H^{5''}), 3.82–2.95 (m, 5H, H^{2''-H^{4''}}). **Overall Ratio (x;y;z)** = 22:7:71 (Average Mw per unit = 161.10 g.mol⁻¹).

¹³C NMR (101 MHz, CDCl₃) δ ppm: **Initiator**, not observed. **Section x**, 171.9 (C¹⁰), 154.8 (C¹²), 143.9 (ArC), 143.7 (ArC), 141.3 (ArC), 128.4 (C⁶), 127.7 (C⁷), 127.1 (ArCH), 125.1 (ArCH), 120.0 (ArCH), 79.4* (C³), 78.7* (C³), 77.6, 76.2, 71.1, 69.9 (C² & C⁴ & C⁵), 67.0 (C¹³), 53.5 (C⁹), 47.2 (C¹⁴), 35.3 (C⁸). **Section y**, 128.2 (C^{6'}), 116.7 (H^{7'}), 79.4* (C^{3'}), 78.7* (C^{3'}), 77.6, 76.1, 71.1, 69.9 (C^{2'} & C^{4'} & C^{5'}). **Section z**, 128.5 (C^{6''}), 79.4* (C^{3''}), 78.7* (C^{3''}), 77.6, 76.1, 71.1, 69.9 (C^{2''} & C^{4''} & C^{5''}).

Polyether:α-Oxymethylbenzene-ω-hydroxy-poly [methyl (2*S*)-2-[(9-fluoren-9-yl)methoxy]carbonyl)amino]-6-(oxiran-2-ylmethoxy)hex-4-enoate]-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-*graft*-2.15

Formula: $C_7H_7O(C_{25}H_{27}NO_6)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of p(AGE) (100 mg, 0.88 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 was added Fmoc-ALG-OMe (1.25 g, 3.50 mmol, 4.00 equiv) and Hoveyda-Grubbs' second-generation catalyst (28 mg, 0.044 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethylsulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-*graft*-2.15 as a viscous brown oil (133 mg, 80%).

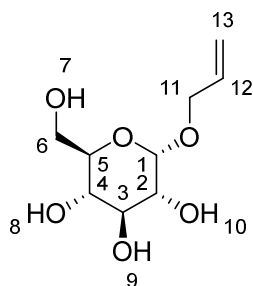
IR (ν , cm^{-1}): 3041, 2920, 2720, 1775, 1601, 1595, 1455, 1375, 1322, 1299, 1221, 1103, 989.

1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 4.61 (s, 2H, H^1), **Section x**, 7.79 (br s, 2H, Ar-H), 7.55 (br s, 2H, Ar-H), 7.45–7.15 (br m, 4H, Ar-H), 5.75 (br s, 1H, H^6), 5.65 (br s, 1H, H^7), 4.50 (br s, 2H, H^{13}), 4.45–4.38 (m, 2H, H^9 and H^{14}), 4.22–4.19 (m, 2H, H^5), 4.12–4.09 (m, 1H, NH), 3.79–2.90 (m, 5H, H^{2-4}), 3.65 (s, 3H, H^{21}), 2.61–2.58 (m, 2H, H^8). **Section y**, 5.89–5.81 (m, 1H, H^6), 5.32–5.28 (m, 1H, $H^{7trans'}$), 5.18–5.15 (m, 1H, $H^{7cis'}$), 4.05–3.92 (m, 2H, H^5), 3.79–2.90 (m, 5H, H^2-H^4), **Section z**, 5.89–5.81 (m, 1H, $H^{6''}$), 4.05–3.92 (m, 2H, H^5''), 3.79–2.90 (m, 5H, $H^{2''-H^4''}$). **Overall Ratio (x;y;z)** = 26:3:71 (Average M_w per unit = 188.17 $g \cdot mol^{-1}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 164.8 (C^{10}), 154.8 (C^{12}), 144.0 (ArC), 143.8 (ArC), 141.5 (ArC), 128.7 (C^6), 127.5 (C^7), 127.1 (ArCH), 125.2 (ArCH), 120.4 (ArCH), 79.4* (C^3), 78.7* (C^3), 77.7, 72.7, 70.9, 68.9 (C^2 & C^4 & C^5), 67.0 (C^{13}), 53.5 (C^9), 50.2 (C^{21}), 47.2 (C^{14}), 35.8 (C^8). **Section y**, 128.2 (C^6), 116.7 (H^7), 79.4*

(C^{3'}), 78.7* (C^{3'}), 77.7, 72.7, 70.9, 68.9 (C^{2'} & C^{4'} & C^{5'}). **Section z**, 128.5 (C^{6''}), 79.4* (C^{3''}), 78.7* (C^{3''}), 77.7, 72.7, 70.9, 68.9 (C^{2''} & C^{4''} & C^{5''}).

(2*S*,3*R*,4*S*,5*S*,6*R*)-2-(Allyloxy)-6-(hydroxymethyl)tetrahydro-2*H*-pyran-3,4,5-triol^[122]



2.35

Formula: C₉H₁₆O₆

Molecular Weight: 220.22

To a dry flask charged with allyl alcohol (17 mL, 250 mmol, 15 equiv) was added dropwise acetyl chloride (1.5 mL, 22 mmol, 1.3 equiv) at 0 °C, and the resulting mixture was allowed to stir for 5 min. To this solution was added *D*-Glucose (3.00 g, 17 mmol, 1.0 equiv), and the reaction mixture was stirred at 50 °C for 18 h.

The reaction mixture was quenched with sodium bicarbonate (5 g) and filtered through celite using CH₂Cl₂, and the filtrate concentrated under vacuum. The crude material was recrystallised from acetone to yield compound **2.35** as a white solid (1.3 g, 73%).

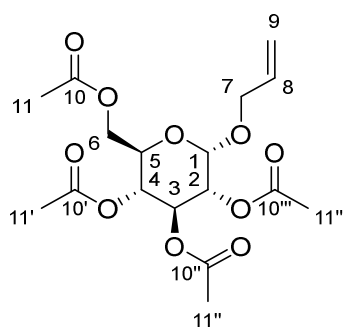
¹H NMR (400 MHz, *D*₂O) δ ppm: 5.98–5.83 (m, 1H, H¹²), 5.30 (d, *J* = 17.3 Hz, 1H, H^{13-trans}), 5.19 (d, *J* = 10.4 Hz, 1H, H^{13-cis}), 4.89 (d, *J* = 3.8 Hz, 1H, H¹), 4.21–4.10 (m, 2H, OCH₂), 3.88–3.73 (m, 2H, OCH₂), 3.73 – 3.13 (m, 5H, H²⁻⁵).

¹³C NMR (101 MHz, *D*₂O) δ ppm: 133.6 (C¹²), 118.2 (C¹³), 101.2 (C¹), 73.1 (CH), 71.9 (CH), 71.3 (CH), 69.6 (CH), 68.5 (C¹¹), 60.5 (C⁶).

[α]_D²⁵ -48.0 (*c* = 0.5, CHCl₃), literature **[α]_D²⁵** -41.4 (*c* = 0.43, CHCl₃).

In agreement with literature data. ^[122]

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(allyloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate^[123]



2.36

Formula: C₁₇H₂₄O₁₀

Molecular Weight: 388.37

To solution of allyl glucose (3.00 g, 13.6 mmol, 1 equiv) and pyridine (22 mL, 270 mmol, 20 equiv) was added DMAP (170 mg, 1.4 mmol, 0.1 equiv) at 0 °C, and the resulting mixture was allowed to stir for 5 min. To this solution was added acetic anhydride (26 mL, 270 mmol, 20 equiv), and the reaction mixture was allowed to warm to RT over 18 h.

The reaction mixture was cooled to 0 °C, quenched with 1 N aqueous HCl (25 ml) and the aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (70:30 PE/EtOAc) to give compound **2.36** as a clear oil (3.7 g, 70%).

¹H NMR (400 MHz, CDCl₃) δ ppm: 5.98–5.80 (m, 1H, H⁸), 5.34 (d, *J* = 17.2 Hz, 1H, H^{9-trans}), 5.25 (d, *J* = 10.4 Hz, 1H, H^{9-cis}), 5.08 (d, *J* = 9.5 Hz, 1H, H¹), 4.34–3.97 (m, 8H, CH²⁻⁷), 2.12 (s, 3H, CH₃), 2.09 (s, 3H, CH₃), 2.05 (s, 3H, CH₃), 2.03 (s, 3H, CH₃).

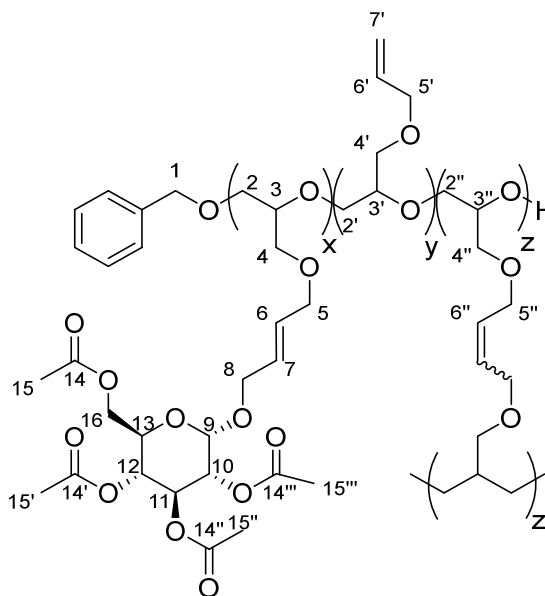
¹³C NMR (101 MHz, CDCl₃) δ ppm: 170.6 (CO), 170.2 (CO), 170.1 (CO), 169.6 (CO), 133.1 (C⁸), 118.2 (C⁹), 94.8 (C¹), 70.7 (CH), 70.1 (CH), 68.8 (OCH₂), 68.5 (CH), 67.3 (CH), 61.9 (OCH₂), 20.7 (CH₃), 20.6 (CH₃), 20.5 (CH₃), 20.4 (CH₃).

HRMS (ESI) for C₁₇H₂₄NaO₁₀: 411.1262, Mass found: 411.1247

[α]_D²⁵ -19.2 (*c* = 1.0, CHCl₃), literature **[α]_D²⁵** -26.1 (*c* = 0.96, CHCl₃).

In agreement with literature data. ^[123]

Polyether: α -oxymethylbenzene- ω -hydroxy-poly[(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(acetoxymethyl)-6-((4-(oxiran-2-ylmethoxy)but-2-en-1-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate]-co-[2-({allyl oxy}methyl)oxirane]-co-1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-2.66

Formula: $C_7H_7O(C_{21}H_{30}O_{12})_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (50 mg, 0.44 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added allyl glucose derivative **46** (680 mg, 1.75 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (13 mg, 0.022 mmol, 0.05 equiv), and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-**2.66** as a brown oil (70 mg, 98%).

IR (ν , cm^{-1}): 3055, 2922, 2872, 1751, 1265, 1089.

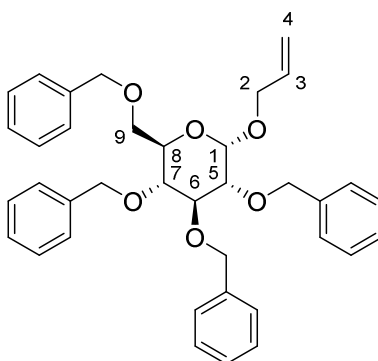
1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 7.35–7.33 (m, 5 H, Ar-H), H^1 not observable. **Section x**, 5.98 (s, 1H, H^6 or H^7), 5.56–5.47 (m, 1H, H^6 or H^7), 5.06–5.03 (m, 1H, H^9), 4.20–4.05 (m, 4H, H^5 and H^8), 3.93–3.29 (m, 11H, H^{2-4} and H^{10-13} and H^{16}), 2.12 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.03 (s, 3H, CH_3). **Section y**, 5.95–5.85 (m, 1H, H^6), 5.28 (d, $J = 17.6$ Hz, 1H, $H^{7'-trans}$), 5.18 (d, $J = 10.7$ Hz, 1H, $H^{7'-cis}$), 4.05–3.95 (m, 2H, H^5), 3.93–3.29 (m, 5H, $H^{2'-4'}$). **Section z**, 5.95–5.85 (m, 1H, H^6), 4.05–3.95 (m, 2H, H^5), 3.93–3.29 (m, 5H, $H^{2''-4''}$). **Overall Ratios (x;y;z)** = 15:30:55 (Average Mw per unit = 163.11 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 170.9 (CO), 170.1 (CO), 170.0 (CO), 169.6 (CO), 125.9 (C^6), 121.4 (C^7), 94.8 (C^9), 79.5* (C^3), 78.7* (C^3), 77.6 (OCH_2), 76.1 (OCH_2), 72.3 (OCH), 70.0 (OCH), 68.8 (OCH_2), 68.2 (OCH_2), 67.3 (OCH), 67.1 (OCH), 66.6 (OCH), 61.7 (OCH_2), 20.8 (CH_3), 20.6 (CH_3), 20.5 (CH_3), 20.1 (CH_3).

Section y, 128.5 (C^{6'}), 116.7 (H^{7'}), 79.5* (C^{3'}), 78.7* (C^{3'}), 77.6, 76.1, 70.0, 68.2 (C^{2'} & C^{4'} & C^{5'}). **Section z**, 128.5 (C^{6''}), 79.5* (C^{3''}), 78.7* (C^{3''}), 77.6, 76.1, 70.0, 68.2 (C^{2''} & C^{4''} & C^{5''}).

GPC: $M_n = 7690$, $M_w = 16190$, $\bar{D} = 2.10$.

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-(Allyloxy)-3,4,5-*tris*(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran^[124]



2.39

Formula: C₃₇H₄₀O₆

Molecular Weight: 580.72

To solution of allyl glucose (0.77 g, 3.5 mmol, 1.0 equiv) and TBAB (1.47 g, 4.55 mmol, 1.30 equiv) in aqueous sodium hydroxide solution (33% w/w) at 0 °C, was added dropwise benzyl bromide (5.0 mL, 42 mmol, 12 equiv). The reaction mixture was heated at 55 °C for 18 h.

The reaction mixture was neutralised to pH 7 with 1 N aqueous HCl, then the aqueous phase was extracted with toluene (3 × 25 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (85:15 PE/EtOAc) to give compound **2.39** as a clear oil (1.1 g, 56%).

IR (ν, cm⁻¹): 3063, 3030, 2912, 2866, 1726, 1068.

¹H NMR (400 MHz, CDCl₃) δ ppm: 7.43–7.24 (m, 20H, ArH), 6.06–5.88 (m, 1H, H³), 5.34 (ddd, *J* = 17.4, 3.1, 1.6 Hz, 1H, H^{4-trans}), 5.23 (ddd, *J* = 10.3, 2.7, 1.4 Hz, 1H, H^{4-cis}), 5.02 (d, *J* = 11.0 Hz, 1H, H¹), 4.90–4.42 (m, 8H, ArCH₂), 4.23–4.13 (m, 2H, OCH₂), 4.08–3.99 (m, 2H, OCH₂), 3.90–3.44 (m, 4H, H⁵⁻⁸).

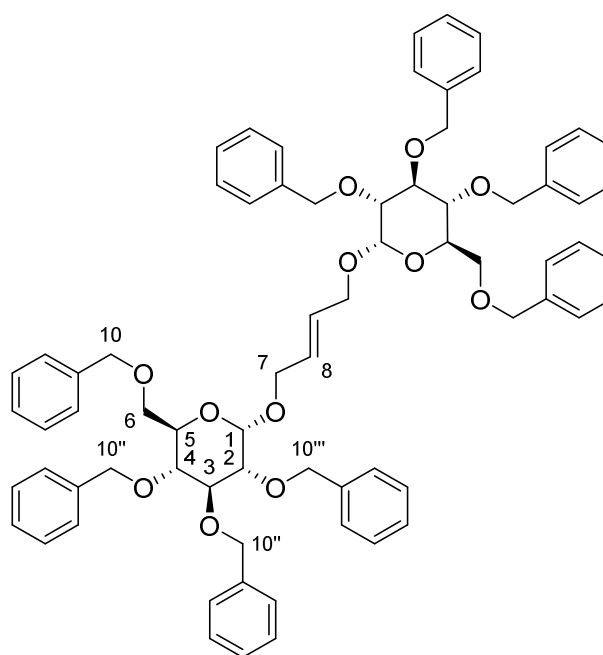
¹³C NMR (101 MHz, CDCl₃) δ ppm: 138.9 (Ar), 138.3 (Ar), 138.3 (Ar), 138.0 (Ar), 133.8 (C³), 128.4 (Ar-H), 128.3 (Ar-H), 128.2 (Ar-H), 128.1 (Ar-H), 127.9 (Ar-H), 127.8 (Ar-H), 127.7 (Ar-H), 127.6 (Ar-H), 127.5 (Ar-H), 118.1 (C⁴), 95.8 (C¹), 82.1 (CH), 79.9 (CH), 77.8 (CH), 77.2 (CH), 75.7 (ArCH₂), 75.1 (ArCH₂), 73.5 (ArCH₂), 73.2 (ArCH₂), 68.5 (OCH₂), 68.2 (OCH₂).

HRMS (ESI) for [C₃₇H₄₀NaO₆]: 603.2717, found: 603.2695

[α]_D²⁵ -150.7 (*c* = 1.0, CHCl₃), literature **[α]_D²⁵** not specified.

In agreement with literature data. ^[124]

(2*S*,3*R*,4*S*,5*R*,6*R*)-2-(Allyloxy)-3,4,5-*tris*(benzyloxy)-6-((benzyloxy)methyl)tetrahydro-2*H*-pyran dimer



2.40

Formula: C₇₂H₇₆O₁₂

Molecular Weight: 1133.39

To a degassed solution of Bn-allyl glucose **2.39** (1.00 g, 1.72 mmol, 1.00 equiv) in CH₂Cl₂ (10 mL) was added Hoveyda-Grubbs' second-generation catalyst (54 mg, 0.086 mmol, 0.05 equiv), and the mixture was stirred at reflux for 16 h.

The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The crude material was purified by column chromatography (90:10 PE/EtOAc) to give compound **2.40** as a clear oil (0.85 g, 87%) with an *E*:*Z* ratio of 20:1.

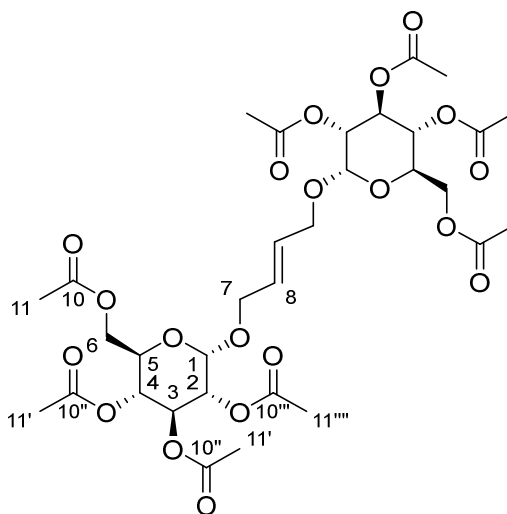
IR (ν, cm⁻¹): 3063, 3030, 2912, 2866, 1726, 1068.

¹H NMR (400 MHz, CDCl₃) δ ppm: 7.40–7.21 (m, 40H, ArH), 5.87–5.75 (m, 2H, H⁸), 5.12–5.01 (m, 2H, H¹), 4.88–4.40 (m, 16H, ArCH₂), 4.21–4.13 (m, 4H, OCH₂), 4.10–4.00 (m, 4H, OCH₂), 3.81–3.40 (m, 8H, H²⁻⁵).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 138.7 (Ar), 138.3 (Ar), 138.2 (Ar), 138.0 (Ar), 131.6 (C⁸), 128.6 (Ar-H), 128.3 (Ar-H), 128.2 (Ar-H), 128.0 (Ar-H), 127.9 (Ar-H), 127.8 (Ar-H), 127.7 (Ar-H), 127.6 (Ar-H), 127.5 (Ar-H), 99.1 (C¹), 82.4 (CH), 79.9 (CH), 77.8 (CH), 77.2 (CH), 75.7 (ArCH₂), 75.1 (ArCH₂), 73.5 (ArCH₂), 73.2 (ArCH₂), 68.5 (OCH₂), 68.0 (OCH₂).

HRMS (ESI) for C₇₂H₇₆NaO₁₂: 1155.5234, found: 1155.5247

(2*R*,3*R*,4*S*,5*R*,6*S*)-2-(Acetoxymethyl)-6-(allyloxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate dimer



2.38

Formula: C₃₂H₄₄O₂₀

Molecular Weight: 748.68

To degassed solution of Ac-allyl glucose **2.36** (1.00 g, 2.57 mmol, 1.00 equiv) in CH₂Cl₂ (15 mL) was added Hoveyda-Grubbs' second-generation catalyst (80 mg, 0.129 mmol, 0.05 equiv), and the mixture was stirred at reflux for 16 h.

The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The crude material was purified by column chromatography (70:30 PE/EtOAc) to give compound **2.38** as a clear oil (0.91 g, 95%) with an *E*:*Z* ratio of 20:1.

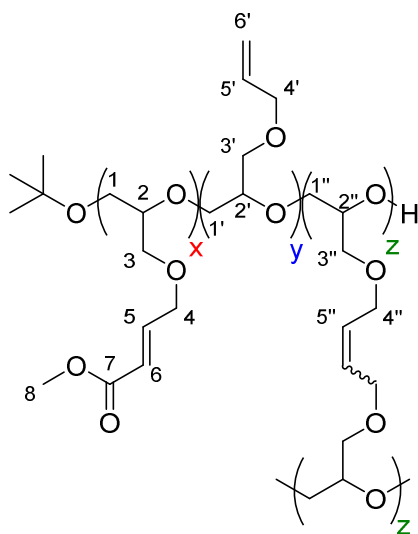
IR (ν, cm⁻¹): 3078, 3005, 2912, 2890, 1746, 1159, 1068.

¹H NMR (400 MHz, CDCl₃) δ ppm: 5.74–5.62 (m, 2H, H⁸), 5.10 (d, *J* = 9.5 Hz, 2H, H¹), 4.40–3.99 (m, 16H, CH²⁻⁷), 2.12 (s, 6H, CH₃), 2.06 (s, 6H, CH₃), 2.01 (s, 6H, CH₃), 1.92 (s, 6H, CH₃).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 170.6 (CO), 170.2 (CO), 170.1 (CO), 169.6 (CO), 131.9 (C⁸), 94.8 (C¹), 70.7 (CH), 70.1 (CH), 68.8 (OCH₂), 68.5 (CH), 66.2 (CH), 61.9 (OCH₂), 20.2 (CH₃), 19.8 (CH₃), 19.2 (CH₃), 18.7 (CH₃).

HRMS (ESI) for C₃₂H₄₄NaO₂₀: 771.2324, found: 771.2345.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl 4-(oxiran-2-ylmethoxy)but-2-enoate]-*co*-[2-({allyl oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-*graft*-MA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (50 mg, 0.44 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added methyl acrylate (0.16 mL, 1.8 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.02 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-*graft*-MA as a brown oil (74 mg, 92%) exclusively as the *E* isomer.

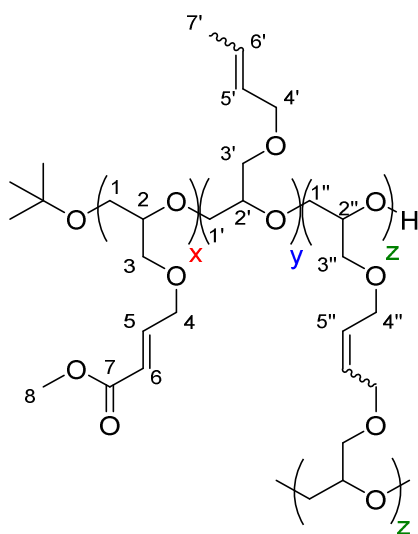
IR (ν , cm^{-1}): 2872, 1720, 1662, 1273, 1109, 729.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.86 (dt, J = 15.8, 4.1 Hz, 1H, H^5), 5.99 (d, J = 15.8 Hz, 1H, H^6), 4.09 (br s, 2H, H^4), 3.76–3.34 (m, 5H, H^{1-3}), 3.66 (s, 3H, H^8). **Section y**, 5.71–5.87 (m, 1H, H^5), 5.59–5.42 (m, 2H, H^6), 4.05–3.95 (m, 2H, H^4), 3.84–3.32 (m, 5H, $H^{1-3'}$). **Section z**, 5.94–5.71 (m, 1H, $H^{5''}$), 4.05–3.95 (m, 2H, $H^{4''}$), 3.84–3.32 (m, 5H, $H^{1''-3''}$). **Overall Ratio (x;y;z)** = 85:5:10 (Average Mw per unit = 173.88 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 166.6 (C^7), 144.7 (C^5), 120.6 (C^6), 79.4* (C^2), 78.7* (C^2), 77.7, 72.8, 70.9, 69.9, 69.4 (C^1 & C^3 & C^4), 51.5 (C^8). **Section y**, 128.2 ($C^{5'}$), 116.7 ($C^{6'}$), 79.4* ($C^{2'}$), 78.7* ($C^{2'}$), 77.7, 72.8, 70.9, 69.9, 69.4 ($C^{1'}$ & $C^{3'}$ & $C^{4'}$). **Section z**, 128.5 ($C^{5''}$), 79.4* ($C^{2''}$), 78.7* ($C^{2''}$), 77.7, 72.8, 70.9, 69.9, 69.4 ($C^{1''}$ & $C^{3''}$ & $C^{4''}$).

GPC: M_n = 13896, M_w = 29295, \bar{D} = 2.11.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl 4-(oxiran-2-ylmethoxy)but-2-enoate]-*co*-[2-({but-2-en-1-yl-oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PCGE-*graft*-MA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_7H_{12}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PCGE (50 mg, 0.39 mmol, 1.0 equiv) in 1 mL of CH_2Cl_2 was added methyl acrylate (0.14 mL, 1.6 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (12 mg, 0.02 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing the PCGE-*graft*-MA as a brown oil (63 mg, 95%).

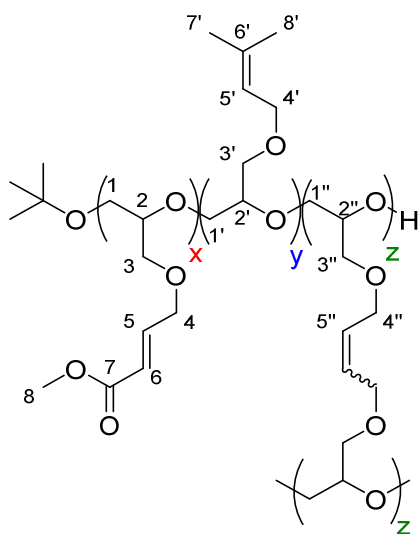
IR (ν , cm^{-1}): 2870, 1720, 1667, 1281, 1102, 745.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.86 (dt, $J = 15.6, 3.5$ Hz, 1H, H^5), 5.99 (d, $J = 15.6$ Hz, 1H, H^6), 4.11–4.08 (m, 2H, H^4), 3.76–3.34 (m, 5H, H^{1-3}), 3.66 (s, 3H, H^8). **Section y**, not observed, **Section z**, 5.94–5.71 (m, 1H, $H^{5''}$), 4.05–3.95 (m, 2H, $H^{4''}$), 3.84–3.32 (m, 5H, $H^{1''-3''}$) **Overall Ratio (x;y;z)** = 80:0:20 (Average M_w per unit = 168.87 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 166.6 (C^7), 144.7 (C^5), 120.6 (C^6), 78.7 (C^2), 71.0, 69.9, 69.3 (C^1 & C^3 & C^4), 51.5 (C^8). **Section y**, not observed. **Section z**, 128.4 ($C^{5''}$), 78.7 ($C^{2''}$), 71.0, 69.9, 69.3 ($C^{1''}$ & $C^{3''}$ & $C^{4''}$).

GPC: $M_n = 13939$, $M_w = 30811$, $\bar{D} = 2.21$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl 4-(oxiran-2-ylmethoxy)but-2-enoate]-*co*-[2-({3-Methylbut-2-en-1-yl-oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PPGE-*graft*-MA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_8H_{14}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PPGE (50 mg, 0.35 mmol, 1.0 equiv) in 0.9 mL of CH_2Cl_2 was added methyl acrylate (0.13 mL, 1.5 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (11 mg, 0.018 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PPGE-*graft*-MA as a brown oil (54 mg, 84%).

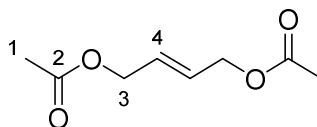
IR (ν , cm^{-1}): 2868, 1719, 1686, 1266, 1199, 756.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.86 (d, $J = 15.7$ Hz, 1H, H^5), 5.99 (d, $J = 15.7$ Hz, 1H, H^6), 4.09 (s, 2H, H^4), 3.76–3.34 (m, 5H, H^{1-3}), 3.65 (s, 3H, H^8). **Section y**, 5.23 (s, 1H, H^5), 4.05–3.95 (m, 2H, H^4), 3.84–3.32 (m, 5H, $H^{1'-3'}$), 1.66 (s, 3H, H^7 or 8), 1.58 (s, 3H, H^7 or 8). **Section z**, 5.75–5.65 (m, 1H, $H^{5''}$), 4.05–3.95 (m, 2H, $H^{4''}$), 3.84–3.32 (m, 5H, $H^{1''-3''}$) **Overall Ratio (x;y;z)** = 95:2:3 (Average Mw per unit = 182.65 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 166.6 (C^7), 144.7 (C^5), 120.6 (C^6), 78.8 (C^2), 71.0, 69.9, 67.8 (C^1 & C^3 & C^4), 51.5 (C^8). **Section y**, not observable, **Section z**, not observable.

GPC: $M_n = 14831$, $M_w = 29745$, $\bar{D} = 2.00$.

(*E*)-But-2-ene-1,4-diyl diacetate^[125]



***E*-2.3**

Formula: C₈H₁₂O₄

Molecular Weight: 172.18

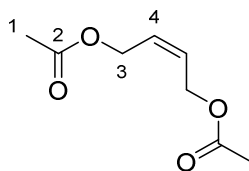
To a solution of allyl acetate (0.40 mL, 3.7 mmol) in 5 mL of degassed benzene was added Grubbs' first-generation catalyst (150 mg, 0.19 mmol, 0.04 equiv) and the mixture was stirred at RT for 14 h. The reaction mixture was concentrated under vacuum and the crude material was purified by column chromatography (7:3 PE/EtOAc) to give compound ***E*-2.3** as the major isomer (*E*:*Z*, 6:1), as a colourless oil (160 mg, 42%). Data for *E* isomer:

¹H NMR (500 MHz, CDCl₃) δ ppm: 5.88 (tt, *J* = 3.0, 1.4 Hz, 2H, H⁴), 4.60 (dd, *J* = 3.0, 1.4 Hz, 4H, H³), 2.10 (s, 6H, H¹)

¹³C NMR (126 MHz, CDCl₃) δ ppm: 170.6 (C²), 128.1 (C⁴), 63.9 (C³), 20.9 (C¹).

In agreement with literature data. ^[125]

(*Z*)-But-2-ene-1,4-diyl diacetate^[126]



Z-2.3

Formula: C₈H₁₂O₄

Molecular Weight: 172.18

To a solution of (*Z*)-but-2-ene-1,4-diol (1.0 mL, 12 mmol) in 70 mL of CH₂Cl₂ was added triethylamine (5.1 mL, 37 mmol, 3.0 equiv) and DMAP (150 mg, 1.22 mmol, 0.10 equiv). The solution was cooled to 0 °C and acetyl chloride (3.5 mL, 48 mmol, 4.0 equiv) was added dropwise over 10 min. The reaction mixture was stirred and allowed to warm to RT overnight.

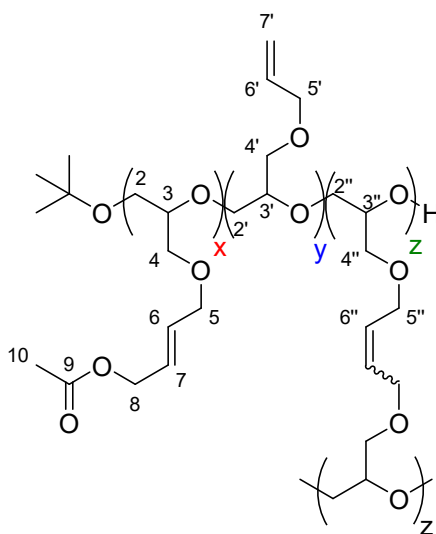
The reaction mixture was quenched with a 1 M aqueous solution of sodium bicarbonate (50 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and reduced under vacuum. The crude material was purified by column chromatography (7:3 PE/EtOAc) to give compound **Z-2.3** as a colourless oil (460 mg, 85%).

¹H NMR (400 MHz, CDCl₃) δ ppm: 5.78 (t, *J* = 4.1 Hz, 2H, H⁴), 4.70 (dd, *J* = 4.0, 1.2 Hz, 4H, H³), 2.09 (s, 6H, H¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 170.7 (C²), 128.0 (C⁴), 60.0 (C³), 20.9 (C¹).

In agreement with literature data. ^[126]

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[(*E*)-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-*co*-[2-({allyl oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PAGE-*graft-AA*

Formula: $C_4H_9O(C_9H_{14}O_4)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (50 mg, 0.44 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added allyl acetate dimer **Z-2.3** (300 mg, 1.7 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.022 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-*graft-AA* as a brown oil (65 mg, 90%) with an *E:Z* ratio of 3:1.

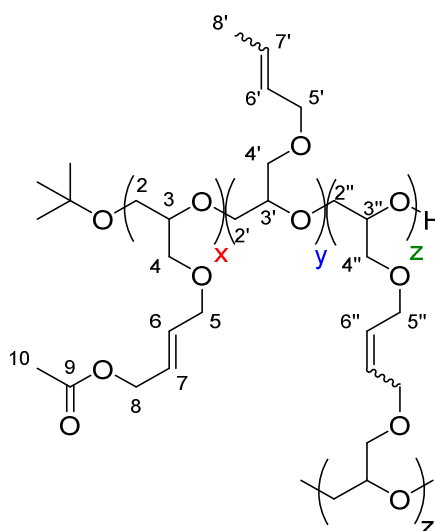
IR (ν , cm^{-1}): 2910, 2868, 1737, 1365, 1230, 1107.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.94–5.71 (m, 2H, H^6 & H^7), 4.55 (d, $J = 4.1$ Hz, 2H, H^8), 4.05–3.95 (m, 2H, H^5), 3.84–3.32 (m, 5H, H^{2-4}), 2.07 (s, 3H, H^{10}). **Section y**, 5.94–5.71 (m, 1H, H^6), 5.25 (d, $J = 17.3$ Hz, 1H, $H^{7-trans}$), 5.16 (d, $J = 10.4$ Hz, 1H, H^{7-cis}), 4.05–3.95 (m, 2H, H^5), 3.84–3.32 (m, 5H, H^{2-4}). **Section z**, 5.94–5.71 (m, 1H, H^6), 4.05–3.95 (m, 2H, H^5), 3.84–3.32 (m, 5H, H^{2-4}). **Overall Ratio (x;y;z)** = 87:4:9 (Average Mw per unit = 163.20 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 170.6 (C^9), 131.1 (C^6), 126.2 (C^7), 79.4* (C^3), 78.8* (C^3), 77.7, 72.7 (C^2 & C^4), 71.0 (C^8), 70.4 (C^5), 20.9 (C^{10}). **Section y**, 128.1 (C^6), 116.7 (C^7), 79.4* (C^3), 78.8* (C^3), 77.7, 72.7, 70.0 (C^2 & C^4 & C^5). **Section z**, 128.6 (C^6), 79.4* (C^3), 78.8* (C^3), 77.7, 72.7, 70.0 (C^2 & C^4 & C^5).

GPC: $M_n = 12315$, $M_w = 18011$, $D = 1.46$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[(*E*)-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-*co*-[2-({but-2-en-1-yl-oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PCGE-*graft-AA*

Formula: $C_4H_9O(C_9H_{14}O_4)_x(C_7H_{12}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PCGE (50 mg, 0.39 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added allyl acetate dimer **Z-2.3** (270 mg, 1.6 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.022 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PCGE-*graft-AA* as a brown oil (51 mg, 83%) with an *E*:*Z* ratio of 3:1.

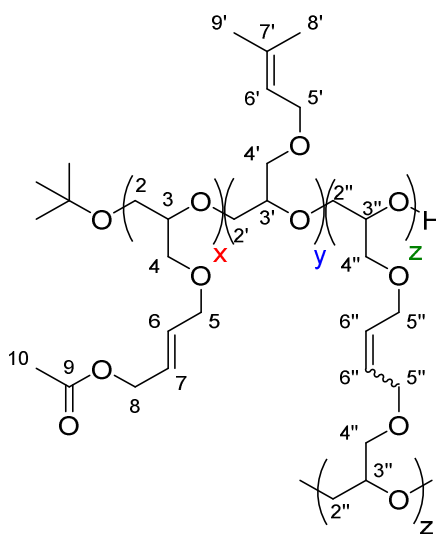
IR (ν , cm^{-1}): 2910, 2868, 1737, 1365, 1230, 1107.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.94–5.65 (m, 2H, H^6 & H^7), 4.55 (d, $J = 4.1$ Hz, 2H, H^8), 4.05–3.95 (m, 2H, H^5), 3.84–3.32 (m, 5H, H^{2-4}), 2.07 (s, 3H, H^{10}). **Section y**, 5.94–5.65 (m, 1H, $H^{7'}$), 5.62–5.51 (m, 1H, $H^{6'}$), 3.94–3.90 (m, 2H, H^5), 3.84–3.32 (m, 5H, H^{2-4}), 1.71 (dd, $J = 6.3, 1.0$ Hz, 3H, H^8). **Section z**, 5.94–5.65 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.84–3.32 (m, 5H, $H^{2''-4''}$). **Overall Ratio (x;y;z)** = 73:12:15 (Average Mw per unit = 155.92 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 170.6 (C^9), 131.1 (C^6), 128.3, (C^7), 78.8 (C^3), 77.2 (C^5), 70.9 (C^8), 70.4, 70.0, 64.2 (C^2 & C^4), 20.9 (C^{10}). **Section y**, 129.1 (C^6), 127.9 (C^7), 78.8 (C^3), 77.2 (C^5), 70.4, 70.0, 64.2 ($C^{2'}$ & $C^{4'}$), 17.5 (C^8). **Section z**, 128.5 ($C^{6''}$), 78.8 ($C^{3''}$), 77.2 ($C^{5''}$), 70.4, 70.0, 64.2 ($C^{2''}$ & $C^{4''}$).

GPC: $M_n = 15590$, $M_w = 30922$, $D = 1.98$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[(*E*)-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-*co*-[2-((3-Methylbut-2-en-1-yl-oxy)methyl)oxirane]-*co*-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PPGE-*graft-AA*

Formula: $C_4H_9O(C_9H_{14}O_4)_x(C_8H_{14}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PPGE (50 mg, 0.35 mmol, 1.0 equiv) in 0.9 mL of CH_2Cl_2 was added allyl acetate **Z-2.3** (240 mg, 1.4 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (11 mg, 0.018 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PPGE-*graft-AA* as a brown oil (52 mg, 95%) with an *E:Z* ratio of 3:1.

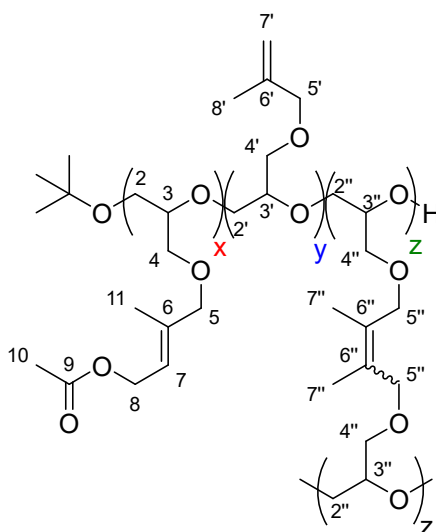
IR (ν , cm^{-1}): 2914, 2861, 1738, 1365, 1228, 1089.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.10 (s, 9H, CH_3). **Section x**, 5.85–5.49 (m, 2H, H^6 & H^7), 4.55 (d, $J = 4.2$ Hz, 2H, H^8), 4.05–3.95 (m, 2H, H^5), 3.84–3.32 (m, 5H, H^{2-4}), 2.00 (s, 3H, H^{10}). **Section y**, 5.24 (t, $J = 6.9$ Hz, 1H, H^6), 4.05–3.95 (m, 2H, H^5), 3.84–3.32 (m, 5H, $H^{2-4'}$), 1.66 (s, 3H, $H^{8'}$ or $9'$), 1.59 (s, 3H, $H^{8'}$ or $9'$). **Section z**, 5.94–5.71 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.84–3.32 (m, 5H, $H^{2''-4''}$). **Overall Ratio (x;y;z)** = 60:30:10 (Average Mw per unit = 155.80 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 170.6 (C^9), 131.1 (C^6), 126.2, (C^7), 78.8 (C^3), 77.2 (C^5), 71.0 (C^8), 70.4, 70.0, 67.8, 64.2 (C^2 & C^4), 20.9 (C^{10}). **Section y**, 136.4 (C^6), 121.4 (C^7), 78.8 (C^3), 77.2 (C^5), 70.4, 70.0, 67.8, 64.2 ($C^{2'}$ & $C^{4'}$), 25.7 ($C^{8'}$ or $9'$), 18.1 ($C^{8'}$ or $9'$). **Section z**, 128.4 ($C^{6''}$), 78.8 ($C^{3''}$), 77.2 ($C^{5''}$), 70.4, 70.0, 67.8, 64.2 ($C^{2''}$ & $C^{4''}$).

GPC: $M_n = 12813$, $M_w = 22594$, $D = 1.76$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[(*E*)-3-methyl-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-co-[2-({2-methylallyl oxy}methyl)oxirane]



PMAGE-*graft-AA*

Formula: $C_4H_9O(C_{10}H_{16}O_4)_x(C_7H_{12}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PMAGE (50 mg, 0.39 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added allyl acetate dimer **Z-2.3** (269 mg, 1.6 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (12 mg, 0.020 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PMAGE-*graft-AA* as a brown oil (62 mg, 97%) with an *E:Z* ratio of 3:1.

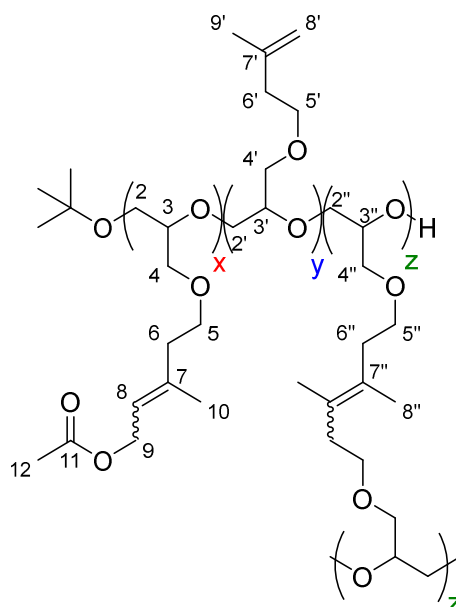
IR (ν , cm^{-1}): 2911, 2862, 2358, 1732, 1448, 1236, 1094, 908, 731.

1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.10 (s, 9H, CH_3). **Section x**, 5.50 (t, $J = 7.0$ Hz, 1H, H^7), 4.55 (d, $J = 7.0$ Hz, 2H, H^8), 3.86 (s, 2H, H^5), 3.64–3.27 (m, 5H, H^{2-4}), 1.98 (s, 3H, H^{10}), 1.64 (s, 3H, H^{11}). **Section y**, 4.93 (s, 1H, $H^{7'a}$), 4.85 (s, 1H, $H^{7'b}$), 3.86 (s, 2H, H^5), 3.70–3.40 (m, 5H, $H^{2'-4'}$), 1.70 (s, 3H, H^8). **Section z**, Not observed, **Overall Ratio (x;y;z)** = 50:50: 0. (Average Mw per unit = 164.00 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: 170.9 (C^9), 138.3 (C^6), 120.4 (C^7), 78.9* (C^3), 78.8* (C^3), 76.7, 76.1 (C^2 & C^4 & C^5), 70.1 (C^8), 69.8, 69.5, 60.8 (C^2 & C^4 & C^5), 20.9 (C^{10}), 14.0 (C^{11}). **Section y**, 142.2 (H^6), 111.9 (H^7), 78.9* (C^3), 78.8* (C^3), 76.7, 76.1, 69.8, 69.5, 60.8 (C^2 & C^4 & C^5), 19.4 (C^8). **Section z**, Not observed,

GPC: $M_n = 15944$, $M_w = 17364$, $D = 1.09$

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[(*E*)-3-methyl-4-(oxiran-2-ylmethoxy)pent-2-en-1-yl acetate]-co-[2-({3-Methylbut-3-en-1-yl-oxy}methyl)oxirane]



PBMGE-*graft-AA*

Formula: $C_4H_9O(C_{11}H_{18}O_4)_x(C_8H_{14}O_2)_y(C_{14}H_{24}O_4)_z$

To a solution of PMBGE (50 mg, 0.35 mmol, 1.0 equiv) in 0.9 mL of toluene was added allyl acetate dimer **Z-2.3** (240 mg, 1.4 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (11 mg, 0.018 mmol, 0.050 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/CH₂Cl₂) furnishing PBMGE-*graft-AA* as a brown oil (55 mg, 95%) with an *E:Z* ratio of 3:1.

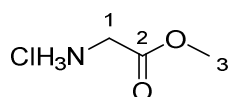
IR (ν , cm⁻¹): 2910, 2864, 2360, 1734, 1230, 1108, 1023, 887.

¹H NMR (500 MHz, CDCl₃) δ ppm: **Initiator**, 1.10 (s, 9H, CH₃). **Section x**, 5.36 (t, *J* = 7.1 Hz, 1H, H⁸), 4.57 (d, *J* = 7.1 Hz, 2H, H⁹), 3.66–3.37 (m, 7H, H²⁻⁵), 2.33–2.24 (m, 2H, H⁶), 2.04 (s, 3H, H¹²), 1.71 (s, 3H, H¹⁰). **Section y**, 4.75 (s, 1H, H^{8a}), 4.70 (s, 1H, H^{8b}), 3.66–3.37 (m, 7H, H²⁻⁵), 2.33–2.24 (m, 2H, H⁶), 1.73 (s, 3H, H⁹). **Section z**, Not observed, **Overall Ratio (x;y;z)** = 35:65:0. (Average Mw per unit = 163.00 g.mol⁻¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: **Section x**: 171.0 (C¹¹), 139.2 (C⁷), 120.9 (C⁸), 78.9 (C³), 78.7, 71.0, 70.1, 69.8 (C² & C⁴ & C⁵ & C⁹), 39.5 (C⁶), 24.1 (C¹²), 14.0 (C¹⁰). **Section y**: 142.8 (C⁷), 111.4 (C⁷), 78.7 (C³), 78.7, 71.0, 70.1, 69.8 (C² & C⁴ & C⁵), 37.8 (C⁶), 22.8 (C⁹). **Section z**: not observed

GPC: *Mn* = 6511, *Mw* = 10054, *D* = 1.54

Methyl glycinate^[127]



2.24a

Formula: C₃H₈NO₂Cl

Molecular Weight: 125.55

To a solution of glycine (5.00 g, 66.6 mmol, 1.00 equiv) in 100 mL of methanol was added dropwise freshly distilled SOCl₂ (5.4 mL, 73 mmol, 1.1 equiv), and the solution was stirred at reflux for 3 h. The reaction mixture was reduced under vacuum to yield compound **2.24a** as a white solid (8.3 g, 99%).

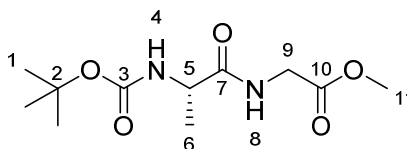
¹H NMR (400 MHz, D₂O) δ ppm: 3.85 (s, 2H, H¹), 3.75 (s, 3H, H³), 3.26 (br s, 3H, NH₃).

¹³C NMR (101 MHz, D₂O) δ ppm: 168.7 (C²), 53.2 (C³), 40.1 (C¹).

Melting Point: 171 °C

In agreement with literature data. ^[127]

Methyl (*tert*-Butoxycarbonyl)-L-alanylglycinate^[128]



2.28

Formula: C₁₁H₂₀N₂O₅

Molecular Weight: 260.29

To a solution of methyl glycinate hydrochloride (1.00 g, 7.96 mmol, 1.00 equiv) in 150 mL of THF was added Boc-Ala-OH (1.51 g, 7.96 mmol, 1.00 equiv) and BOP (3.87 g, 8.76 mmol, 1.10 equiv), and the solution cooled to 0 °C. To this solution was added dropwise DIPEA (3.5 ml, 20 mmol, 2.5 equiv). The solution stirred and allowed to warm to RT over 18 h.

The reaction mixture was quenched with saturated aqueous ammonium chloride then the aqueous phases extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate then brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (70:30 PE/EtOAc) to give compound **2.28** as a clear oil (2.1 g, 99%).

¹H NMR (400 MHz, CDCl₃) δ ppm: 6.58 (br s, 1H, NH), 4.90–4.80 (m, 1H, H⁵), 4.15 (s, 1H, NH), 4.05–3.89 (m, 2H, H⁹), 3.69 (s, 3H, H¹¹), 1.39 (s, 9H, H¹), 1.36–1.25 (m, 3H, H⁶).

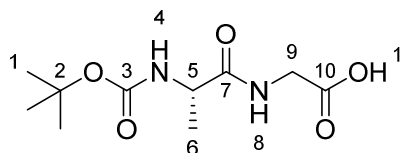
¹³C NMR (126 MHz, CDCl₃) δ ppm: 173.2 (C¹⁰), 170.2 (C⁷), 155.6 (C³), 80.2 (C²), 52.3 (C¹¹), 49.9 (C⁵), 41.1 (C⁹), 28.3 (C¹), 18.3 (C⁶).

HRMS (ESI) for C₁₁H₂₀N₂NaO₅: 283.1264, found: 283.1251.

[α]_D²⁵ +96.7 (*c* = 1.0, CHCl₃), literature **[α]_D²⁵** not specified.

In agreement with literature data. ^[128]

(*tert*-Butoxycarbonyl)-*L*-Alanylglycine^[129]



2.29

Formula: C₁₀H₁₈N₂O₅

Molecular Weight: 246.26

To a stirring solution of Boc-Ala-Gly-OMe (1.00 g, 3.84 mmol, 1.00 equiv) in 20 mL of methanol was added at 0 °C 1 N aqueous NaOH (12 mL, 12 mmol, 3.1 equiv). The solution was stirred and allowed to warm to RT over 18 h.

Methanol was removed under vacuum, and the reaction mixture then acidified with 1 N aqueous HCl to pH 2. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), the organic phases were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by precipitation in PE to yield compound **2.29** as white crystals (620 mg, 65%).

¹H NMR (500 MHz, *DMSO*) δ ppm: 12.55 (br s, 1H, H¹¹), 8.02 (dd, *J* = 5.9, 5.4 Hz, 1H, H⁸), 6.93 (d, *J* = 7.8 Hz, 1H, H⁴), 4.01–3.96 (m, 1H, H⁵), 3.78 (dd, *J* = 17.6, 5.9 Hz, 1H, H⁹), 3.69 (dd, *J* = 17.6, 5.4 Hz, 1H, H⁹), 1.38 (s, 9H, H¹), 1.17 (d, *J* = 7.2 Hz, 3H, H⁶).

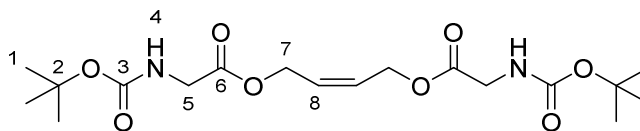
¹³C NMR (126 MHz, *DMSO*) 184.0 (C¹⁰), 173.4 (C⁷ or C³), 169.1 (C⁷ or C³), 78.5 (C²), 49.9 (C⁵), 41.1 (C⁹), 28.7 (C¹), 18.7 (C⁶).

HRMS (ESI) calculated for C₁₀H₁₇N₂O₅: 245.1143, Mass Found: 245.1125.

Melting Point: 69 °C

In agreement with literature data. ^[129]

(*Z*)-But-2-ene-1,4-diyl bis(2-((*tert*-butoxycarbonyl)amino)acetate)



2.24

Formula: C₁₈H₃₀N₂O₈

Molecular Weight: 402.44

To a solution of Boc-Gly-OH (2.80 g, 17.1 mmol, 3.00 equiv) in 25 mL of CH₂Cl₂ was added DMAP (200 mg, 1.71 mmol, 0.30 equiv) and (*Z*)-but-2-ene-1,4-diol (0.47 mL, 5.71 mmol, 1.00 equiv). The solution was cooled to 0 °C and EDCI (3.58 g, 20.0 mmol, 3.50 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 18 h.

Water (100 ml) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 50 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (70:30 PE/EtOAc) to give compound **2.24** as a thick white oil (3.16 g, 100%).

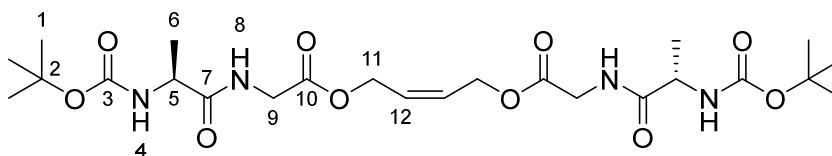
IR (ν, cm⁻¹): 3368, 2978, 2933, 1697, 1510, 1155.

¹H NMR (500 MHz, CDCl₃) δ ppm: 5.77 (t, *J* = 5.2 Hz, 2H, H⁸), 5.08-5.02 (m, 2H, H⁴), 4.76 (d, *J* = 5.2 Hz, 4H, H⁷), 3.93 (d, *J* = 5.8 Hz, 4H, H⁵), 1.45 (s, 18H, H¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 170.1 (C⁶), 155.7 (C³), 128.0 (C⁸), 80.1 (C²), 60.6 (C⁷), 42.4 (C⁵), 28.3 (C¹).

HRMS (ESI) – for C₁₈H₃₀N₂O₈Na: 425.1894, found: 425.1876.

(*Z*)-But-2-ene-1,4-diyl bis(2-((*S*)-2-((*tert*-Butoxycarbonyl)amino)propanamido)acetate)



2.30

Formula: C₂₄H₄₀N₄O₁₀

Molecular Weight: 544.60

To a solution of Boc-Ala-Gly-OH (1.00 g, 4.06 mmol, 3.00 equiv) in 25 mL of CH₂Cl₂ was added DMAP (48 mg, 0.39 mmol, 0.30 equiv) and (*Z*)-but-2-ene-1,4-diol (0.11 mL, 1.4 mmol, 1.0 equiv). The solution was cooled to 0 °C and EDCI (0.85 g, 4.4 mmol, 3.3 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 18 h.

Water (100 ml) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 25 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (65:35 PE/Acetone) to give compound **2.30** as a thick white oil (760 mg, 99%).

IR (ν, cm⁻¹): 3316, 2980, 2933, 2249, 1750, 1664, 1508, 1376, 1163, 729.

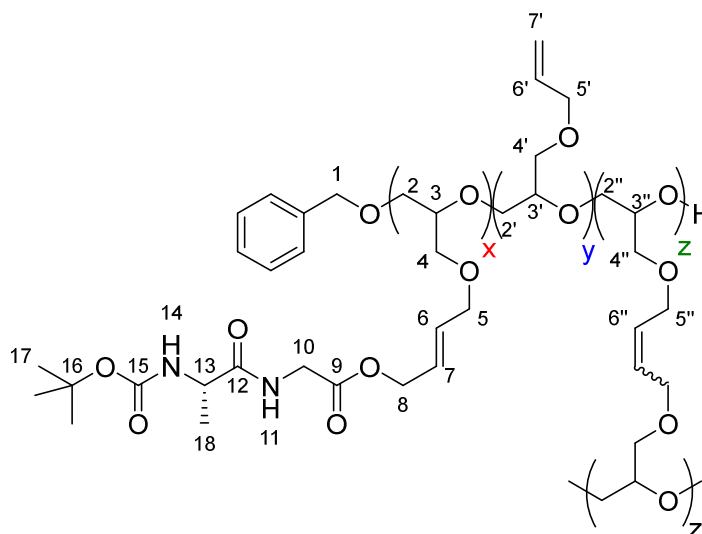
¹H NMR (500 MHz, CDCl₃) δ ppm: 6.86–8.78 (m, 2H, NH), 5.80 (t, *J* = 5.2 Hz, 2H, H¹²), 5.13 (br s, 2H, NH), 4.78 (d, *J* = 5.2 Hz, 4H, H¹¹), 4.31–4.21 (m, 2H, H⁵), 4.11 (dd, *J* = 18.2, 5.4 Hz, 2H, H^{9a}), 4.04 (dd, *J* = 18.2, 5.2 Hz, 2H, H^{9b}), 1.47 (s, 18H, H¹), 1.40 (d, *J* = 7.1 Hz, 6H, H⁶).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 173.4 (C¹⁰), 169.5 (C⁷), 155.6 (C³), 128.0 (C¹²), 80.0 (C²), 60.6 (C¹¹), 49.9 (C⁵), 41.2 (C⁹), 28.3 (C¹), 18.4 (C⁶).

M/S (ESI) – for C₂₄H₄₁N₄NaO₁₀: 567.2642, found: 567.2659.

[α]_D²⁵ +5.8 (*c* = 1.0, CHCl₃).

Polyether: α -oxymethylbenzene- ω -hydroxy-poly[(*E*)-4-(oxiran-2-ylmethoxy)but-2-en-1-yl (tert-butoxycarbonyl)-L-alanylglycinate]-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-**2.30**

Formula: $C_7H_7O(C_{17}H_{28}N_2O_7)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (25 mg, 0.22 mmol, 1.0 equiv) in 1 mL of CH_2Cl_2 was added diester **2.30** (480 mg, 0.88 mmol, 4.0 equiv) and Hoveyda-Grubbs' second-generation catalyst (7 mg, 0.011 mmol, 0.05 equiv), and the mixture was stirred at reflux for 8 h. The reaction mixture was quenched with tosylmethyl isocyanide (20 mg, 0.1 mmol, 0.45 equiv) and stirred for 5 min. The reaction mixture was then purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-graft-**2.30** as a brown oil (35 mg, 87%). (Average Mw per unit = 181.73 g.mol⁻¹).

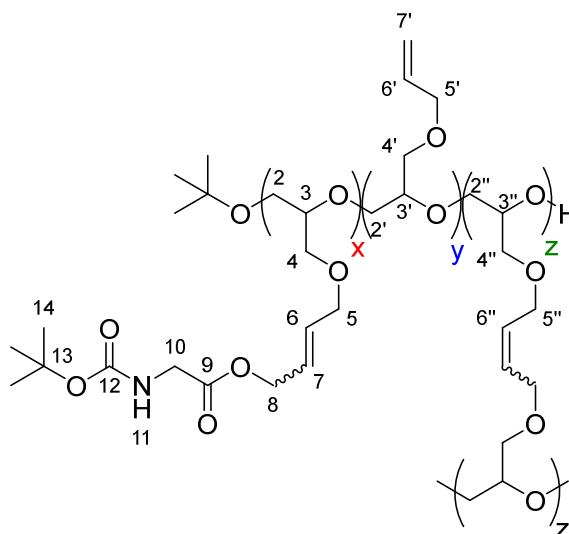
IR (ν , cm⁻¹): 3400, 3055, 2983, 2931, 2868, 1747, 1680, 1265.

¹H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, none observed **Section x**, 7.10 (br s, 1H, NH), 5.84–5.63 (m, 2H, H⁶ and H⁷), 5.38–5.35 (m, 1H, NH), 4.57–4.53 (m, 2H, H⁸), 4.22–4.19 (m, 1H, H¹³), 4.05–3.85 (m, 4H, H⁵ and H¹⁰), 3.77–3.19 (m, 5H, H²⁻⁴), 1.37 (s, 9H, H¹⁷), 1.31 (d, J = 7.0 Hz, 3H, H¹⁸). **Section y**, not observed. **Section z**, 5.84–5.63 (m, 1H, H^{6''}), 4.05–3.85 (m, 2H, H^{5''}), 3.77–3.19 (m, 5H, H^{2''-4''}) **Overall Ratio (x;y;z)** = 30:0:70 (Average Mw per unit = 181.73 g.mol⁻¹).

¹³C NMR (126 MHz, $CDCl_3$) δ ppm: 173.3 (C⁹), 169.6 (C¹²), 155.6 (C¹⁵), 131.8 (C⁶), 129.5 (C⁷), 80.1 (C¹⁶), 78.9 (C³), 71.5, 70.8, 70.0, 65.1 (C² & C⁴ & C⁵), 49.9 (C¹³), 41.2 (C¹⁰), 28.4 (C¹⁷), 18.5 (C¹⁸). **Section y**, not observed, **Section z**, 125.4 (C^{6''}), 78.9 (C^{3''}), 71.5, 70.8, 70.0, 65.1 (C^{2''} & C^{4''} & C^{5''}).

GPC: M_n = 9855, M_w = 16556, \bar{D} = 1.68

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(oxiran-2-ylmethoxy)but-2-en-1-yl] (*tert*-butoxycarbonyl)glycinate]-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]



PAGE-graft-Gly-Boc

Formula: $C_4H_9O(C_{14}H_{23}NO_6)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PAGE (50 mg, 0.44 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added Boc-Gly-dimer **2.24** (350 mg, 0.88 mmol, 2.00 equiv), Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.022 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing the PAGE-graft-Gly-Boc as a brown oil (67 mg, 94%) with an *E:Z* ratio of 3:1.

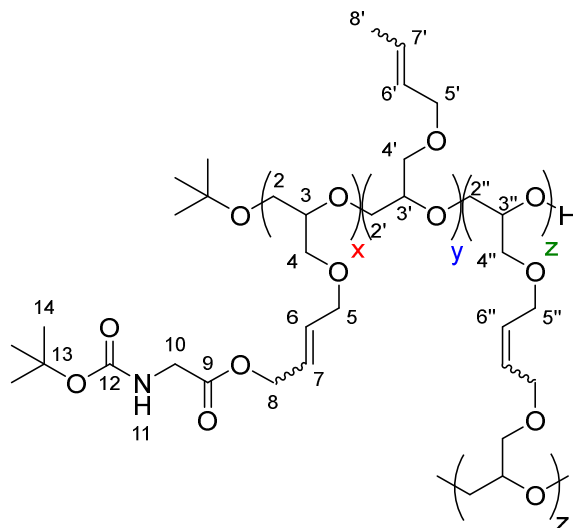
IR (ν , cm^{-1}): 3459, 3015, 2970, 2864, 1728, 1365, 1228.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.90–5.70 (m, 2H, $H^{6\&7}$), 5.04 (s, 1H, H^{11}), 4.76 (d, $J = 5.3$ Hz, 2H, H^8), 3.94 (d, $J = 5.8$ Hz, 2H, H^5), 3.84–3.32 (m, 7H, $H^{2-4\&10}$), 1.45 (s, 9H, H^{14}). **Section y**, 5.90–5.70 (m, 1H, H^6), 5.24 (d, $J = 17.3$ Hz, 1H, $H^{7'-trans}$), 5.14 (d, $J = 10.4$ Hz, 1H, $H^{7'-cis}$), 4.03–3.93 (m, 2H, H^5), 3.84–3.32 (m, 5H, $H^{2'-4'}$). **Section z**, 5.90–5.70 (m, 1H, $H^{6''}$), 4.03–3.93 (m, 2H, $H^{5''}$), 3.84–3.32 (m, 5H, $H^{2''-4''}$). **Overall Ratio (x;y;z)** = 30:7:63 (Average Mw per unit = 161.38 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 170.1 (C^9), 155.8 (C^{12}), 131.7 (C^6), 125.5 (C^7), 79.9 (C^{13}), 78.8* (C^3), 77.4* (C^3), 77.0, 76.7, 70.8 (C^2 and C^4), 70.5 (C^5), 65.0 (C^8), 42.4 (C^{10}), 28.3 (C^{14}). **Section y**, 129.3 (C^6), 116.7 (C^7), 78.8* (C^3), 77.4* (C^3), 77.0, 76.7, 70.8 (C^2 and C^4 and C^5). **Section z**, 128.7 ($C^{6''}$), 78.8* ($C^{3''}$), 77.4* ($C^{3''}$), 77.0, 76.7, 70.8 ($C^{2''}$ and $C^{4''}$ and $C^{5''}$).

GPC:. $M_n = 22704$, $M_w = 41057$, $D = 1.81$

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(oxiran-2-ylmethoxy)but-2-en-1-yl] (*tert*-butoxycarbonyl)glycinate-*co*-[2-({but-2-en-1-yl-oxy}methyl)oxirane]-*co*-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PCGE-*graft*-Gly-Boc

Formula: $C_4H_9O(C_{14}H_{23}NO_6)_x(C_7H_{12}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PCGE (50 mg, 0.39 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added Boc-Gly-dimer **2.24** (310 mg, 0.78 mmol, 2.00 equiv), Hoveyda-Grubbs' second-generation catalyst (12 mg, 0.020 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PCGE-*graft*-Gly-Boc as a brown oil (58 mg, 82%) with an *E:Z* ratio of 3:1.

IR (ν , cm^{-1}): 3455, 3017, 2971, 2865, 1738, 1366, 1217.

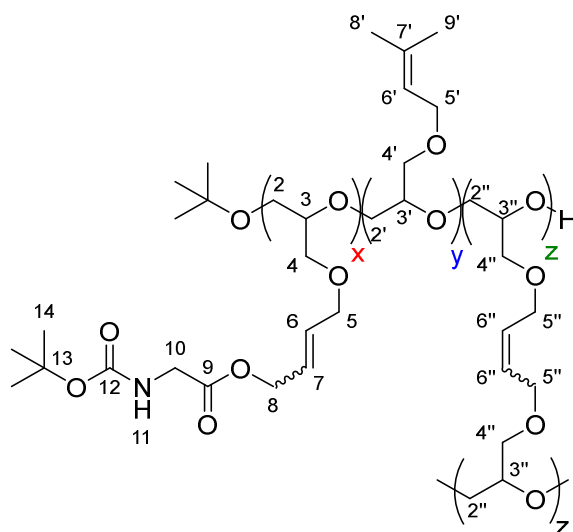
1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.88–5.78 (m, 2H, $H^{6\&7}$), 5.20 (s, 1H, H^{11}), 4.62 (d, $J = 5.0$ Hz, 2H, H^8), 3.93 (d, $J = 5.8$ Hz, 2H, H^5), 3.75–3.30 (m, 7H, $H^{2-4\&10}$), 1.45 (s, 9H, H^{14}). **Section y**, 5.78–5.64 (m, 1H, H^7), 5.62–5.51 (m, 1H, H^6), 4.03–3.93 (m, 2H, H^5), 3.75–3.30 (m, 5H, $H^{2'-4'}$), 1.69 (d, $J = 6.5$, 3H, $H^{8'}$). **Section z**, 5.88–5.78 (m, 1H, $H^{6''}$), 4.03–3.93 (m, 2H, $H^{5''}$), 3.75–3.30 (m, 5H, $H^{2''-4''}$) **Overall Ratio** (**x;y;z**) = 40:7:53 (Average Mw per unit = 182.50 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 170.1 (C^9), 155.8 (C^{12}), 131.7 (C^6), 125.5 (C^7), 79.9 (C^{13}), 78.8* (C^3), 77.4* (C^3), 77.0, 72.8, 70.8 (C^2 and C^4), 70.5 (C^5), 65.0 (C^8), 42.4 (C^{10}), 28.3 (C^{14}). **Section y**, 129.0 ($C^{6'}$), 127.9 ($C^{7'}$), 78.8* ($C^{3'}$), 77.4* ($C^{5'}$), 77.0, 72.8,

70.8 (C^{2'} and C^{4'} and C^{5'}), 17.9 (C^{8'}). **Section z**, 128.7 (C^{6''}), 78.8* (C^{3''}), 77.4* (C^{3''}), 77.0, 72.8, 70.8 (C^{2''} and C^{4''} and C^{5''}).

GPC: $M_n = 17089$, $M_w = 29319$, $\bar{D} = 1.72$

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(oxiran-2-ylmethoxy)but-2-en-1-yl] (*tert*-butoxycarbonyl)glycinate]-co-[2-((3-Methylbut-2-en-1-yl-oxy)methyl)oxirane]-co-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]



PPGE-*graft*-Gly-Boc

Formula: $C_4H_9O(C_{14}H_{23}NO_6)_x(C_8H_{14}O_2)_y(C_{10}H_{16}O_4)_z$

To a solution of PPGE (50 mg, 0.35 mmol, 1.0 equiv) in 0.9 mL of CH_2Cl_2 was added Boc-Gly-dimer **2.24** (280 mg, 0.70 mmol, 2.0 equiv), Hoveyda-Grubbs' second-generation catalyst (11 mg, 0.018 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PPGE-*graft*-Gly-Boc as a brown oil (63 mg, 95%) with an *E:Z* ratio of 3:1.

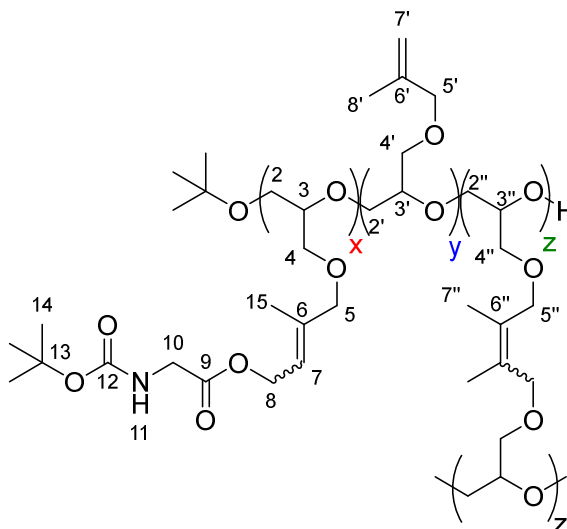
IR (ν , cm^{-1}): 3455, 3017, 2970, 2864, 1738, 1366, 1228.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.89–5.72 (m, 2H, $H^{6\&7}$), 5.41–5.11 (m, 1H, H^{11}), 4.63 (d, $J = 5.1$ Hz, 2H, H^8), 3.90 (d, $J = 5.5$ Hz, 2H, H^5), 3.79–3.38 (m, 7H, $H^{2-4\&10}$), 1.45 (s, 9H, H^{14}). **Section y**, 5.41–5.11 (m, 1H, H^6), 4.03–3.93 (m, 2H, H^5), 3.79–3.38 (m, 5H, $H^{2'-4'}$), 1.72 (s, 3H, H^8 or H^9), 1.63 (s, 3H, H^8 or H^9). **Section z**, 5.89–5.72 (m, 1H, $H^{6''}$), 4.03–3.93 (m, 2H, $H^{5''}$), 3.79–3.38 (m, 5H, $H^{2''-4''}$) **Overall Ratio** (**x;y;z**) = 38:27:35 (Average Mw per unit = 187.85 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 170.1 (C^9), 155.8 (C^{12}), 131.7 (C^6), 125.5 (C^7), 79.9 (C^{13}), 78.8* (C^3), 77.4* (C^3), 77.0, 76.7, 72.8, 70.8 (C^2 and C^4), 70.5 (C^5), 65.0 (C^8), 42.4 (C^{10}), 28.3 (C^{14}). **Section y**, 136.2 (C^7), 121.3 (C^6), 78.8* (C^3), 77.4* (C^5), 77.0, 76.7, 72.8, 70.8 ($C^{2'}$ and $C^{4'}$ and C^5), 25.8 (C^8 or C^9), 18.1 (C^8 or C^9). **Section z**, 128.7 ($C^{6''}$), 78.8* ($C^{3''}$), 77.4* ($C^{3''}$), 77.0, 76.7, 72.8, 70.8 ($C^{2''}$ and $C^{4''}$ and $C^{5''}$).

GPC: $M_n = 16445$, $M_w = 30314$, $D = 1.84$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(oxiran-2-ylmethoxy)3-methyl-but-2-en-1-yl] (*tert*-butoxycarbonyl)glycinate]-co-[2-({2-Methylallyl oxy}methyl)oxirane]



PMAGE-graft-Gly-Boc

Formula: $C_4H_9O(C_{15}H_{25}NO_6)_x(C_7H_{12}O_2)_y(C_{12}H_{20}O_4)_z$

To a solution of PMAGE (50 mg, 0.39 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added Boc-Gly-dimer **2.24** (310 mg, 0.78 mmol, 2.00 equiv), Hoveyda-Grubbs' second-generation catalyst (12 mg, 0.020 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PMAGE-graft-Gly-Boc as a brown oil (70 mg, 97%) with an *E:Z* ratio of 3:1.

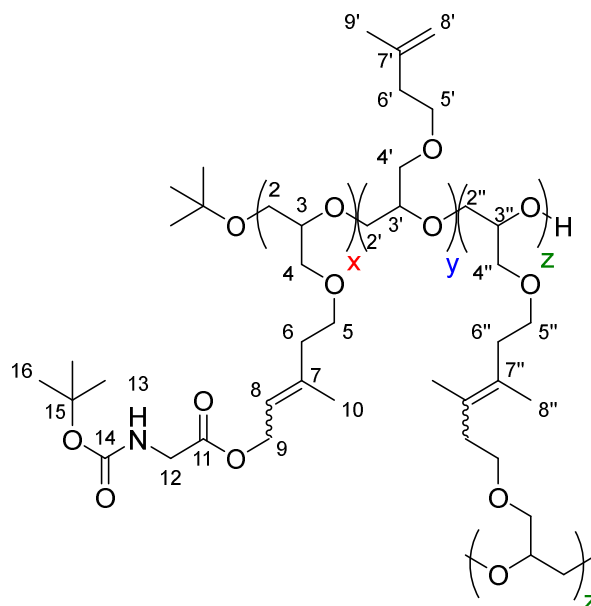
IR (ν , cm^{-1}): 3450, 2917, 2868, 2360, 1268, 1162, 1090.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 5.56 (t, $J = 6.9$ Hz, 1H, H^7), 5.15 (s, 1H, H^{11}), 4.70 (d, $J = 6.9$ Hz, 2H, H^8), 3.88–3.80 (m, 2H, H^5), 3.70–3.36 (m, 7H, $H^{2-4\&10}$), 1.68 (s, 3H, H^{15}), 1.45 (s, 9H, H^{14}). **Section y**, 4.93 (s, 1H, $H^{7'a}$), 4.85 (s, 1H, $H^{7'b}$), 3.88–3.80 (m, 2H, H^5), 3.70–3.36 (m, 5H, $H^{2'-4'}$), 1.70 (s, 3H, H^8). **Section z**, not observed. **Overall Ratio (x;y;z)** = 30:70:0 (Average Mw per unit = 184.10 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 170.3 (C^9), 155.7 (C^{12}), 139.1 (C^6), 119.6 (C^7), 79.8 (C^{13}), 78.8 (C^3), 76.0, 75.2, 70.1, 69.8 (C^2 and C^4 and C^5), 61.5 (C^8), 42.4 (C^{10}), 28.3 (C^{14}), 21.5 (C^{15}). **Section y**, 142.2 (H^6), 111.9 (H^7), 78.8 ($C^{3'}$), 76.0, 75.2, 70.1, 69.8 ($C^{2'}$ and $C^{4'}$ and C^5), 19.4 (C^8). **Section z**, Not observed.

GPC: $M_n = 19016$, $M_w = 20688$, $\bar{D} = 1.09$

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(oxiran-2-ylmethoxy)3-methyl-pent-2-en-1-yl] (*tert*-butoxycarbonyl)glycinate]-co-[2-({3-Methylbut-3-en-1-yl-oxy}methyl)oxirane]



PBMGE-graft-Gly-Boc

Formula: $C_4H_9O(C_{16}H_{27}NO_6)_x(C_8H_{14}O_2)_y(C_{14}H_{24}O_4)_z$

To a solution of PMBGE (50 mg, 0.35 mmol, 1.0 equiv) in 0.9 mL of toluene was added Boc-Gly-dimer **2.24** (280 mg, 0.70 mmol, 2.0 equiv), Hoveyda-Grubbs' second-generation catalyst (11 mg, 0.018 mmol, 0.050 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/CH₂Cl₂) furnishing PBMGE-graft-Gly-Boc as a brown oil (59 mg, 90%) with an *E:Z* ratio of 3:1.

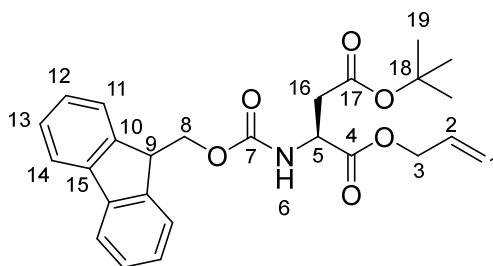
IR (ν , cm⁻¹): 3460, 2932, 2865, 2355, 1718, 1365, 1269, 1111, 1031, 887.

¹H NMR (500 MHz, CDCl₃) δ ppm: **Initiator**, 1.17 (s, 9H, CH₃). **Section x**, 5.36 (t, *J* = 7.0 Hz, 1H, H⁸), 5.12 (s, 1H, H¹³), 4.65 (d, *J* = 7.0 Hz, 2H, H⁹), 3.67–3.40 (m, 9H, H^{2-5&12}), 2.32–2.25 (m, 2H, H⁶), 1.71 (s, 3H, H¹⁰), 1.45 (s, 9H, H¹⁶). **Section y**, 4.76 (s, 1H, H^{8'a}), 4.70 (s, 1H, H^{8'b}), 3.67–3.40 (m, 7H, H^{2'-5'}), 2.32–2.25 (m, 2H, H^{6'}), 1.74 (s, 3H, H^{9'}). **Section z**, Not observed, **Overall Ratio (x;y;z)** = 24:76:0 (Average Mw per unit = 186.40 g.mol⁻¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: **Section x**: 170.9 (C¹¹), 155.7 (C¹⁴), 138.3 (C⁷), 120.9 (C⁸), 78.9 (C³), 78.7 (C⁵), 78.5 (C¹⁵), 71.0, 70.1, 69.8 (C² & C⁴ & C⁹), 42.5 (C¹²), 39.5 (C⁶), 24.1 (C¹⁶), 14.0 (C¹⁰). **Section y**: 142.2 (C^{7'}), 111.9 (C^{8'}), 78.9 (C^{3'}), 71.0, 70.1, 69.8 (C^{2'} & C^{4'} & C^{5'}), 37.6 (C^{6'}), 19.4 (C^{9'}). **Section z**: not observed.

GPC: *Mn* = 7664, *Mw* = 11517, *D* = 1.50

1-Allyl 4-(*tert*-butyl) (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-aspartate^[130]



3.40

Formula: C₂₆H₂₉NO₆

Molecular Weight: 451.52

To a solution of Fmoc-Asp(O*t*Bu)-OH (1.00 g, 2.43 mmol, 1.00 equiv) in 12 mL of CH₂Cl₂ was added DMAP (60 mg, 0.45 mmol, 0.20 equiv) and allyl alcohol (0.20 mL, 2.9 mmol, 1.2 equiv). The solution was cooled to 0 °C and EDCI (0.56 g, 2.9 mmol, 1.2 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 4 h.

Water (12 ml) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (75:25 PE/Et₂O) to give compound **3.40** as a thick clear oil (720 mg, 66%).

IR (ν, cm⁻¹): 3440, 2966, 1725, 1514, 1463, 1375, 1322.

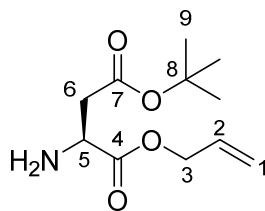
¹H NMR (400 MHz, CDCl₃) δ ppm: 7.69 (d, *J* = 7.5 Hz, 2H, H¹⁴), 7.56–7.50 (m, 2H, H¹¹), 7.33 (t, *J* = 7.5 Hz, 2H, H¹³), 7.24 (t, *J* = 7.5 Hz, 2H, H¹⁴), 5.83 (ddt, *J* = 16.3, 10.7, 5.7 Hz, 1H, H²), 5.74 (d, *J* = 8.3 Hz, 1H, H⁶), 5.26 (dd, *J* = 17.2, 1.5 Hz, 1H, H^{1trans}), 5.18 (dd, *J* = 10.4, 1.2 Hz, 1H, H^{1cis}), 4.67–4.50 (m, 3H, H^{3&5}), 4.35 (dd, *J* = 10.5, 7.2 Hz, 1H, H^{8a}), 4.27 (dd, *J* = 10.5, 7.2 Hz, 1H, H^{8b}), 4.18 (t, *J* = 7.2 Hz, 1H, H⁹), 2.90 (dd, *J* = 16.9, 4.7 Hz, 1H, H^{16a}), 2.71 (dd, *J* = 16.9, 4.6 Hz, 1H, H^{16b}), 1.38 (s, 9H, H¹⁹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 170.6 (C⁴ or ¹⁷), 170.0 (C⁴ or ¹⁷), 156.0 (C⁷), 143.9 (ArC), 141.3 (ArC), 131.5 (C²), 127.7 (ArCH), 127.1 (ArCH), 125.2 (ArCH), 120.0 (ArCH), 118.8 (C¹), 81.9 (C¹⁸), 67.3 (C⁸), 66.3 (C³), 50.6 (C⁵), 47.1 (C⁹), 37.8 (C¹⁶), 28.1 (C¹⁹).

[α]_D²⁵ -12.5 (*c* = 1.0, CHCl₃), literature **[α]_D²⁵** -19.0 (*c* = 1.0, CHCl₃).

In agreement with literature data. ^[130]

1-Allyl 4-(*tert*-butyl)-*L*-aspartate^[130]



3.37

Formula: C₁₁H₁₉NO₄

Molecular Weight: 229.28

To a solution of piperidine (2 mL) in DMF (8 mL) was added dropwise Fmoc-Asp(O*t*Bu)-Oallyl **3.40** (1.00 g, 2.21 mmol, 1.0 equiv) in 2 mL of DMF. The reaction mixture was stirred for 5 min. Brine (10 ml) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL), the combined organic phases were washed with saturated aqueous LiCl (10 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (75:25 PE/Et₂O) to give compound **3.37** as a yellow oil (205 mg, 41%).

¹H NMR (400 MHz, CDCl₃) δ ppm: 5.98–5.85 (m, 1H, H²), 5.33 (dd, *J* = 17.0, 1.1 Hz, 1H, H^{1trans}), 5.26 (dd, *J* = 10.5, 1.0 Hz, 1H, H^{1cis}), 4.64 (d, *J* = 5.8 Hz, 2H, H³), 3.78 (dd, *J* = 6.8, 4.9 Hz, 1H, H⁵), 2.74 (dd, *J* = 16.4, 4.9 Hz, 1H, H^{6a}), 2.66 (dd, *J* = 16.4, 6.8 Hz, 1H, H^{6b}), 1.75 (s, 2H, NH), 1.45 (s, 9H, H⁹).

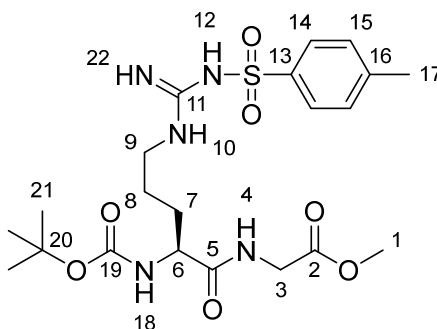
¹³C NMR (101 MHz, CDCl₃) δ ppm: 174.1 (C⁷), 170.3 (C⁴), 131.8 (C²), 118.6 (C¹), 81.2 (C⁸), 65.8 (C³), 51.4 (C⁵), 40.1 (C⁶), 28.1 (C⁹).

HRMS (ESI) – for C₁₁H₁₇NNaO₄: 226.1050, found: 226.1045.

[α]_D²⁵ +87.1 (*c* = 1.0, CHCl₃), literature **[α]_D²⁵** not specified.

In agreement with literature data. ^[130]

Methyl *N*²-(*tert*-Butoxycarbonyl)-*N*^w-tosyl-L-arginylglycinate



3.45

Formula: C₂₁H₃₃N₅O₇S

Molecular Weight: 499.58

To a solution of Boc-Arg(Tos)-OH (1.00 g, 2.33 mmol, 1.00 equiv) in 12 mL of THF was added H-Gly-OMe.HCl (300 mg, 2.33 mmol, 1.00 equiv) and BOP (1.14 g, 2.57 mmol, 1.1 equiv). The solution was stirred while DIPEA (1.0 ml, 5.8 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred for 18 h at RT.

The reaction mixture was concentrated under vacuum, then redissolved in EtOAc (20 mL). The organic phase was washed with saturated aqueous NH₄Cl, a saturated aqueous solution of sodium bicarbonate then brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (96:4 CH₂Cl₂/MeOH) to give compound **3.45** as a white foam (720 mg, 92%).

IR (ν, cm⁻¹): 3330, 3010, 2490, 1741, 1655, 822.

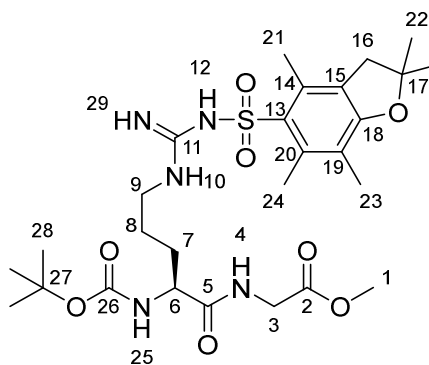
¹H NMR (400 MHz, CDCl₃) δ ppm: 7.78 (d, *J* = 7.0 Hz, 2H, H¹⁴), 7.42 (br s, 1H, NH), 7.26 (d, *J* = 7.0 Hz, 2H, H¹⁵), 6.41 (br s, 1H, NH), 5.55 (br s, 1H, NH), 4.31 (br s, 1H, NH), 4.10 (dd, *J* = 17.2, 5.9 Hz, 1H, H^{3a}), 3.95 (dd, *J* = 17.2, 5.6 Hz, 1H, H^{3b}), 3.73 (s, 3H, H¹), 3.44-3.34 (m, 2H, NH and H⁶), 3.29-3.21 (m, 2H, H⁹), 2.42 (s, 3H, H¹⁷), 1.89-1.85 (m, 1H, H^{7a}), 1.66-1.58 (m, 3H, H^{7b} and H⁸), 1.44 (s, 9H, H²¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 177.7 (C²), 172.9 (C⁵), 157.0 (C¹¹ or C¹⁹), 156.0 (C¹¹ or C¹⁹), 142.1 (ArC), 140.6 (ArC), 129.3 (C¹⁴), 126.0 (C¹⁵), 77.2 (C²⁰), 53.5 (C⁶), 52.3 (C¹), 41.1 (C³ or C⁹), 41.0 (C³ or C⁹), 30.3 (C⁷), 28.3 (C²¹), 25.16 (C⁸), 21.4 (C¹⁷).

M/S (ESI) – for C₂₁H₃₃N₅O₇SNa: 522.1993, found: 522.1999.

[α]_D²⁵ -11.6 (*c* = 1.0, CHCl₃).

Methyl *N*²-(*tert*-Butoxycarbonyl)-*N*^w-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-*L*-arginylglycinate



3.49

Formula: C₂₇H₄₃N₅O₈S

Molecular Weight: 597.73

To a solution of Boc-Arg(Pbf)-OH (2.00 g, 3.80 mmol, 1.00 equiv) in 20 mL of THF was added H-Gly-OMe.HCl (520 mg, 4.18 mmol, 1.10 equiv) and BOP (1.85 g, 4.18 mmol, 1.1 equiv). The solution was stirred while DIPEA (1.3 mL, 7.60 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred for 18 h at RT.

The reaction mixture was concentrated under vacuum, then redissolved in EtOAc (50 mL). The organic phase was washed with a saturated aqueous solution of NH₄Cl, then sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (97.5:2.5 CH₂Cl₂/MeOH) to give compound **3.49** as a white foam (1.50 g, 66%).

IR (ν, cm⁻¹): 3317, 2978, 2360, 2152, 2021, 1967, 1534, 1175, 748.

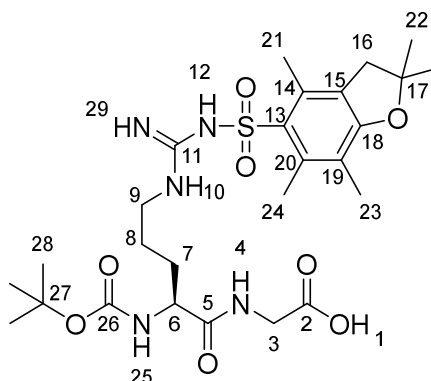
¹H NMR (400 MHz, CDCl₃) δ ppm: 7.48 (s, 1H, NH), 6.25 (s, 1H, NH), 6.07 (s, 1H, NH), 5.63 – 5.45 (m, 1H, NH), 4.28 (s, 1H, NH), 4.09 (dd, *J* = 17.9, 5.6 Hz, 1H, H^{3a}), 3.93 (dd, *J* = 17.9, 5.3 Hz, 1H, H^{3b}), 3.73 (s, 3H, H¹), 3.32-3.25 (m, 3H, H⁶ and H¹⁶), 2.99-2.91 (m, 2H, H⁹), 2.58 (s, 3H, H²¹ or H²³ or H²⁴), 2.51 (s, 3H, H²¹ or H²³ or H²⁴), 2.10 (s, 3H, H²¹ or H²³ or H²⁴), 1.97–1.83 (m, 1H, H^{7a}), 1.67–1.61 (m, 3H, H^{7b} and H⁸), 1.47 (s, 6H, H²²), 1.42 (s, 9H, H²⁸).

¹³C NMR (126 MHz, CDCl₃) δ ppm: 172.9 (C²), 170.7 (C⁵), 158.8 (C¹¹ or C¹⁸ or C²⁶), 156.4 (C¹¹ or C¹⁸ or C²⁶), 155.7 (C¹¹ or C¹⁸ or C²⁶), 138.4 (ArC), 132.3 (ArC), 125.7 (ArC), 124.7 (ArC), 117.5 (ArC), 86.4 (C¹⁷), 77.2 (C²⁷), 53.5 (C⁶), 52.3 (C¹), 43.3 (C⁹), 41.1 (C³), 40.5 (C¹⁶), 30.6 (C⁷), 28.6 (C²² or C²⁸), 28.4 (C²² or C²⁸), 25.1 (C⁸), 19.3 (C²¹ or C²³ or C²⁴), 17.9 (C²¹ or C²³ or C²⁴), 12.5 (C²¹ or C²³ or C²⁴).

HRMS (ESI) – for C₂₇H₄₃N₅NaO₈S: 620.2725, found: 620.2698.

[α]_D²⁵ +9.5 (*c* = 1.0, CHCl₃).

N²-(*tert*-Butoxycarbonyl)-N^w-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-*L*-arginylglycine



3.50

Formula: C₂₆H₄₁N₅O₈S

Molecular Weight: 583.70

To a stirring solution of Boc-Arg(Pbf)-Gly-OMe **3.49** (1.50 g, 2.51 mmol, 1.00 equiv) in 10 mL of methanol was added at 0 °C, 1 N NaOH in methanol (12 mL, 12 mmol, 3.1 equiv). The solution was stirred and allowed to warm to RT over 4 h.

10 mL of water was then added and the methanol was removed under vacuum. The reaction mixture then acidified with 1 N aqueous HCl to pH 2. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL), the organic phases were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by precipitation column chromatography (95:5 CH₂Cl₂/MeOH) to give compound **3.50** as a white foam (1.10 g, 75%).

IR (v, cm⁻¹): 3287, 2970, 1681, 1543, 1365, 1250, 1175, 1103.

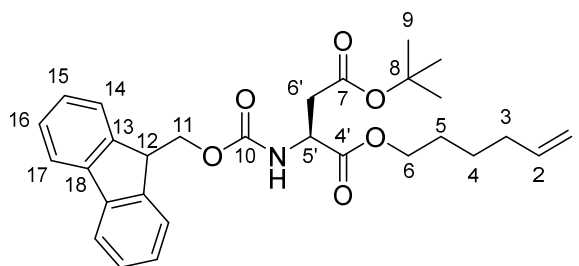
¹H NMR (500 MHz, DMSO-*d*₆) δ 12.84 (br s, 1H, H¹), 7.88 (t, *J* = 5.6 Hz, 1H, H⁴), 6.97 (s, 1H, H¹⁰), 6.91 (d, *J* = 8.3 Hz, 1H, H²⁵), 6.51 (s, 2H, NH), 3.92 (td, *J* = 8.3, 4.8 Hz, 1H, H⁶), 3.69 (dd, *J* = 17.4, 5.6 Hz, 1H, H^{3a}), 3.62 (dd, *J* = 17.4, 5.4 Hz, 1H, H^{3b}), 3.04–2.99 (m, 2H, H⁹), 2.97 (s, 2H, H¹⁶), 2.51 (s, 3H, H²¹ or H²³ or H²⁴), 2.49 (s, 3H, H²¹ or H²³ or H²⁴), 2.43 (s, 3H, H²¹ or H²³ or H²⁴), 1.68–1.56 (m, 1H, H^{7a}), 1.49 – 1.30 (m, 18H, H^{7b} & H⁸ & H²² & H²⁸).

¹³C NMR (126 MHz, DMSO-*d*₆) δ ppm: 172.4 (C⁵), 172.0 (C²), 157.9 (C¹¹ or C¹⁸ or C²⁶), 156.6 (C¹¹ or C¹⁸ or C²⁶), 155.7 (C¹¹ or C¹⁸ or C²⁶), 137.7 (ArC), 134.6 (ArC), 131.9 (ArC), 124.8 (ArC), 116.7 (ArC), 86.7 (C¹⁷), 78.5 (C¹⁷), 54.3 (C⁶), 42.9 (C⁹), 42.0 (C³), 40.6 (C¹⁶), 29.8 (C⁷), 28.8 (C²² or C²⁸), 28.7 (C²² or C²⁸), 25.9 (C⁸), 19.4 (C²¹ or C²³ or C²⁴), 18.1 (C²¹ or C²³ or C²⁴), 12.7 (C²¹ or C²³ or C²⁴).

HRMS (CI) – for C₂₆H₄₀N₅O₈S: 582.2603, found: 582.2597.

[α]_D²⁵ +52.5 (*c* = 1.0, CHCl₃).

4-(*tert*-Butyl) 1-(hex-5-en-1-yl) (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-aspartate



3.46

Formula: C₂₉H₃₅NO₆

Molecular Weight: 493.60

To a solution of Fmoc-Asp(O*t*Bu)-OH (5.71 g, 13.9 mmol, 1.00 equiv) in 50 mL of CH₂Cl₂ was added DMAP (340 mg, 2.78 mmol, 0.20 equiv) and 5-hexen-1-ol (2.00 mL, 16.7 mmol, 1.20 equiv). The solution was cooled to 0 °C and EDCI (4.00 g, 20.9 mmol, 1.50 equiv) was added. The reaction mixture was stirred and allowed to warm to RT over 18 h.

Water (100 ml) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 50 mL), the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (80:20 PE/Et₂O) to give compound **3.46** as a thick clear oil (6.28 g, 92%).

IR (ν, cm⁻¹): 3460, 2812, 1731, 1719, 1693, 1462, 1375, 1319, 877.

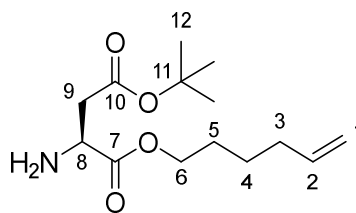
¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.5 Hz, 2H, H¹⁷), 7.61 (t, *J* = 7.5 Hz, 2H, H¹⁴), 7.41 (t, *J* = 7.5 Hz, 2H, H¹⁶), 7.32 (t, *J* = 7.5 Hz, 2H, H¹⁵), 5.85–5.70 (m, 1H, H²), 5.01 (d, *J* = 17.1 Hz, 1H, H^{1trans}), 4.96 (d, *J* = 10.0 Hz, 1H, H^{1cis}), 4.60 (dt, *J* = 9.0, 4.4 Hz, 1H, H⁵), 4.43 (dd, *J* = 10.9, 6.9 Hz, 1H, H^{11a}), 4.35 (dd, *J* = 10.9, 6.9 Hz, 1H, H^{11b}), 4.26 (t, *J* = 6.9 Hz, 1H, H¹²), 4.23–4.11 (m, 2H, H⁶), 2.96 (dd, *J* = 16.9, 4.7 Hz, 1H, H^{6a}), 2.79 (dd, *J* = 16.9, 4.5 Hz, 1H, H^{6b}), 2.12–2.08 (m, 2H, H³), 1.72–64 (m, 4H, H⁴ and H⁵), 1.42 (m, 9H, H⁹).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 170.9 (C^{4'} or 7), 170.0 (C^{4'} or 7), 156.0 (C¹⁰), 143.7 (C¹³ or C¹⁸), 141.3 (C¹³ or C¹⁸), 138.1 (C²), 127.7 (C¹⁶), 127.1 (C¹⁵), 125.1 (C¹⁴), 120.0 (C¹⁷), 115.0 (C¹), 81.8 (C⁸), 67.3 (C¹¹), 65.7 (C⁶), 50.6 (C⁵), 47.1 (C¹²), 37.8 (C⁶), 33.2 (C³), 28.1 (C⁴ or C⁵), 27.9 (C⁴ or C⁵), 25.1 (C⁹).

HRMS (ESI) – for C₂₉H₃₅NNaO₆: 516.2357, found: 516.2341.

[α]_D²⁵ -28.4 (*c* = 1.0, CHCl₃).

4-(*tert*-Butyl) 1-(hex-5-en-1-yl)-L-aspartate



3.47

Formula: C₁₄H₂₅NO₄

Molecular Weight: 271.36

To a solution of piperidine (10 mL) in DMF (15 mL) was added dropwise Fmoc-Asp(O*t*Bu)-O-hexyl **3.46** (4.00 g, 8.10 mmol, 1.0 equiv) in 15 mL of DMF. The reaction mixture was stirred for 5 min. Brine (50 mL) was then added and the aqueous phase extracted with CH₂Cl₂ (3 × 10 mL), the combined organic phases were washed with saturated aqueous LiCl (10 mL), dried over magnesium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (95:5 CH₂Cl₂/MeOH) to give compound **3.47** as a yellow oil (2.00 g, 91%).

IR (ν, cm⁻¹): 3356, 2978, 2361, 1745, 1505, 1450, 1149.

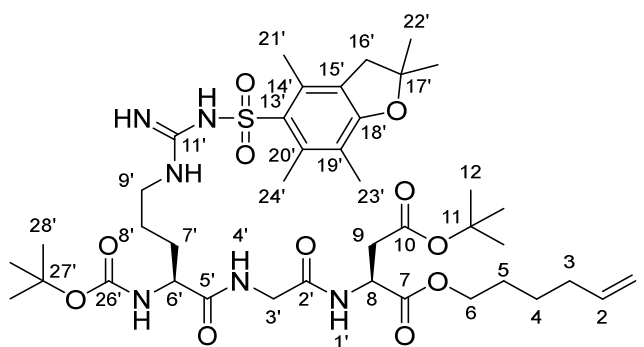
¹H NMR (400 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 17.1, 10.2, 6.7 Hz, 1H, H²), 5.04 (d, *J* = 17.1 Hz, 1H, H^{1trans}), 4.99 (d, *J* = 10.2 Hz, 1H, H^{1cis}), 4.18-4.14 (m, 2H, H⁶), 3.76 (t, *J* = 6.3 Hz, 1H, H⁸), 2.74 (dd, *J* = 16.2, 6.3 Hz, 1H, H^{9a}), 2.66 (dd, *J* = 16.2, 6.3 Hz, 1H, H^{9b}), 2.13-2.07 (m, 2H, H³), 1.84–1.62 (m, 4H, H⁴ or H⁵ and NH₂), 1.54–1.40 (m, 11H, H⁴ or H⁵ and H¹²).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 174.5 (C⁷ or C¹⁰), 170.4 (C⁷ or C¹⁰), 138.2 (C²), 114.9 (C¹), 81.2 (C¹¹), 65.1 (C⁶), 51.4 (C⁸), 40.1 (C⁹), 33.2 (C³), 28.1 (C⁴ or C⁵), 28.0 (C⁴ or C⁵), 25.1 (C¹²).

HRMS (CI) – for C₁₄H₂₆NO₄: 272.1856, found: 272.1879.

[α]_D²⁵ -44.8 (*c* = 1.0, CHCl₃).

4-(*tert*-Butyl) 1-(hex-5-en-1-yl) *N*²-(*tert*-butoxycarbonyl)-*N*^w-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-L-arginylglycyl-L-aspartate



3.44

Formula: C₄₀H₆₄N₆O₁₁S

Molecular Weight: 837.04

To a solution of Boc-Arg(Pbf)-Gly-OH **3.50** (1.10 g, 1.88 mmol, 1.00 equiv) in 20 mL of THF was added H-Asp(OtBu)O-hex **3.47** (610 mg, 2.26 mmol, 1.20 equiv) and BOP (1.00 g, 2.26 mmol, 1.2 equiv). The solution was stirred while DIPEA (0.82 mL, 4.7 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred for 18 h at RT.

The reaction mixture was concentrated under vacuum, then redissolved in EtOAc (50 mL). The organic phase was washed with a saturated aqueous solution of NH₄Cl, then saturated aqueous sodium bicarbonate then brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (98:2 CH₂Cl₂/MeOH) to give compound **3.44** as a white foam (1.57 mg, 75%).

IR (ν, cm⁻¹): 3321, 3108, 2970, 2363, 1748, 1680, 1505, 1452, 1365, 1232, 1182, 1155.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.48 (s, 1H, H^{4'}), 7.17 (d, *J* = 8.1 Hz, 1H, H^{1'}), 6.27 (s, 2H, NH), 6.13 (s, 1H, NH), 5.78 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H, H^{2'}), 5.57 (d, *J* = 8.0 Hz, 1H, NH), 5.02 (dd, *J* = 17.1, 1.9 Hz, 1H, H^{1trans}), 4.98 (dd, *J* = 10.2, 2.0 Hz, 1H, H^{1cis}), 4.79 (dt, *J* = 8.1, 4.9 Hz, 1H, H⁸), 4.29-4.24 (m, 1H, H^{6'}), 4.19-4.08 (m, 2H, H⁶), 4.05 (dd, *J* = 16.7, 5.7 Hz, 1H, H^{3a'}), 3.96 (dd, *J* = 16.7, 5.7 Hz, 1H, H^{3b'}), 3.28 (s, 2H, H^{16'}), 2.99-2.95 (m, 2H, H^{9'}), 2.90 (dd, *J* = 17.0, 4.9 Hz, 1H, H^{9a'}), 2.76 (dd, *J* = 17.0, 4.9 Hz, 1H, H^{9b'}), 2.60 (s, 3H, H^{21'} or H^{23'} or H^{24'}), 2.53 (s, 3H, H^{21'} or H^{23'} or H^{24'}), 2.11 (s, 3H, H^{21'} or H^{23'} or H^{24'}), 2.10-2.06 (m, 2H, H³), 1.92 (d, *J* = 7.1 Hz, 1H, H^{7'a}), 1.73-1.55 (m, 7H, H^{7'b} & H^{8'} & H⁴ & H⁵), 1.48 (s, 6H, H²²), 1.45-1.40 (m, 18H, H¹² & H²⁸).

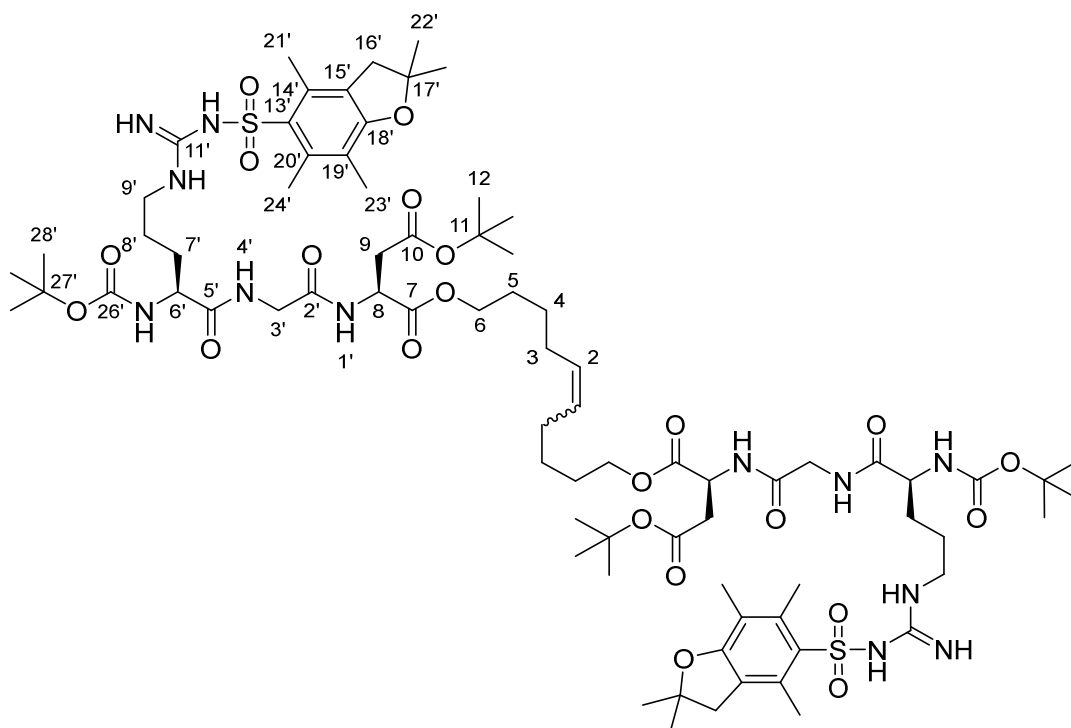
¹³C NMR (101 MHz, CDCl₃) δ ppm: 170.8 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 170.0 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 169.2 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 169.1 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 158.7 (C^{11'} or C^{18'} or C^{26'}), 156.4 (C^{11'} or C^{18'} or C^{26'}), 155.9 (C^{11'} or C^{18'} or C^{26'}), 138.4 (ArC), 138.1 (C²), 132.9 (ArC), 132.3 (ArC), 124.6 (ArC), 117.5 (ArC), 115.0 (C¹), 86.3 (C^{17'}), 81.9 (C¹¹), 77.2 (C^{27'}), 65.9 (C⁶), 53.7 (C^{6'}), 48.9 (C⁸), 43.3 (C⁹), 42.9 (C³), 40.4 (C^{16'}), 37.3 (C⁹), 33.2 (C³), 30.2 (C⁷),

28.6 (C^{22'} or C^{28'}), 28.4 (C^{22'} or C^{28'}), 28.0 (C⁴ or C⁵), 27.9 (C⁴ or C⁵), 25.1 (C^{8'}), 25.0 (C¹²), 19.3 (C^{21'} or C^{23'} or C^{24'}), 17.9 (C^{21'} or C^{23'} or C^{24'}), 12.5 (C^{21'} or C^{23'} or C^{24'}).

HRMS (ESI) – for C₄₀H₆₄N₆NaO₁₁S: 859.4246, found: 859.4209.

[α]_D²⁵ -93.2 (*c* = 1.0, CHCl₃).

RGD-hexenyl-dimer



3.51

Formula: C₇₈H₁₂₄N₁₂O₂₂S₂

Molecular Weight: 1646.03

To a solution of RGD-hexenyl **3.44** (500 mg, 0.57 mmol, 1.0 equiv) in 3.0 mL of CH₂Cl₂ was added Hoveyda-Grubbs' second-generation catalyst (19 mg, 0.030 mmol, 0.050 equiv) and the mixture was stirred at reflux for 16 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by column chromatography, (98:2 CH₂Cl₂/MeOH) to give compound **3.51** as a white foam (350 mg, 75%) in an *E:Z* ratio of 3:1.

IR (v, cm⁻¹): 3330, 3112, 2970, 2363, 1748, 1628, 1505, 1452, 1367, 1232, 1182, 989.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.50 (br s, 2H, H^{4'}), 7.42-7.31 (m, 2H, H^{1'}), 6.33-6.23 (m, 4H, NH), 6.16 (br s, 2H, NH), 5.75-5.70 (m, 2H, H²), 5.39-5.32 (m, 2H, NH), 4.89-4.74 (m, 2H, H⁸), 4.26-4.21 (m, 2H, H^{6'}), 4.19-4.08 (m, 4H, H⁶), 4.02-3.94 (m, 4H, H³), 3.26 (br s, 4H, H^{16'}), 2.99-2.92 (m, 4H, H^{9'}), 2.90 (d, *J* = 17.0 Hz, 2H, H^{9a}), 2.74 (dd, *J* = 17.0 Hz, 2H, H^{9b}), 2.58 (s, 6H, H^{21'} or H^{23'} or H^{24'}), 2.51 (s, 6H, H^{21'} or H^{23'} or H^{24'}), 2.09 (s, 6H, H^{21'} or H^{23'} or H^{24'}), 2.06-1.96 (m, 4H, H³), 1.96-1.85 (m, 2H, H^{7'a}), 1.76-1.53 (m, 14H, H^{7'b} & H^{8'} & H⁴ & H⁵), 1.46 (s, 12H, H²²), 1.45-1.38 (m, 36H, H¹² & H^{28'}).

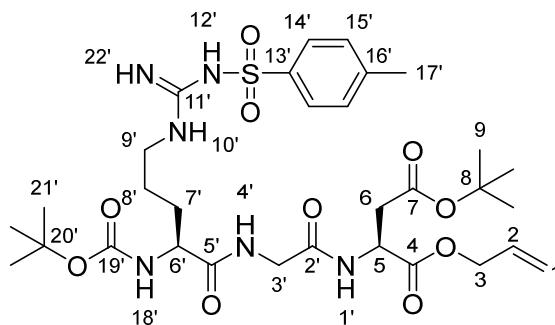
¹³C NMR (101 MHz, CDCl₃) δ ppm: 171.8 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 170.8 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 170.0 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 169.1 (C⁷ or C¹⁰ or C^{2'} or C^{5'}), 158.7 (C^{11'} or C^{18'} or C^{26'}),

156.4 (C^{11'} or C^{18'} or C^{26'}), 154.7 (C^{11'} or C^{18'} or C^{26'}), 138.4 (ArC), 132.9 (ArC), 132.3 (ArC), 130.1 (C²), 124.4 (ArC), 117.4 (ArC), 86.3 (C^{17'}), 81.9 (C¹¹), 77.2 (C^{27'}), 65.9 (C⁶), 53.7 (C^{6'}), 48.9 (C⁸), 43.3 (C⁹), 42.9 (C^{3'}), 40.4 (C^{16'}), 37.3 (C⁹), 32.9 (C³), 30.2 (C^{7'}), 28.6 (C^{22'} or C^{28'}), 28.4 (C^{22'} or C^{28'}), 28.0 (C⁴ or C⁵), 27.9 (C⁴ or C⁵), 25.1 (C^{8'}), 25.0 (C¹²), 19.3 (C^{21'} or C^{23'} or C^{24'}), 17.9 (C^{21'} or C^{23'} or C^{24'}), 12.5 (C^{21'} or C^{23'} or C^{24'}).

HRMS (ESI) – for C₇₈H₁₂₄N₁₂NaO₂₂S₂: 1667.8292, found: 1667.8281.

[α]_D²⁵ +8.5 (*c* = 1.0, CHCl₃).

1-Allyl 4-(*tert*-Butyl) *N*²-(*tert*-butoxycarbonyl)-*N*^w-tosyl-*L*-arginylglycyl-*L*-aspartate



3.35

Formula: C₃₁H₄₈N₆O₁₀S

Molecular Weight: 696.82

To a solution of Boc-Arg(Tos)-Gly-OH **3.36** (1.06 g, 2.18 mmol, 1.00 equiv) in 12.5 mL of THF was added H-Asp(OtBu)O-allyl **3.37** (500 mg, 2.18 mmol, 1.20 equiv) and BOP (1.10 g, 2.50 mmol, 1.1 equiv). The solution was stirred while DIPEA (1.00 mL, 5.34 mmol, 2.5 equiv) was added dropwise. The reaction mixture was stirred for 18 h at RT.

The reaction mixture was concentrated under vacuum, then redissolved in EtOAc (50 mL). The organic phase was washed with a saturated aqueous solution of NH₄Cl, then saturated aqueous sodium bicarbonate then brine, dried over sodium sulfate, filtered and concentrated under vacuum. The crude material was purified by column chromatography (98:2 CH₂Cl₂/MeOH) to give compound **3.44** as a white foam (1.20 mg, 79%).

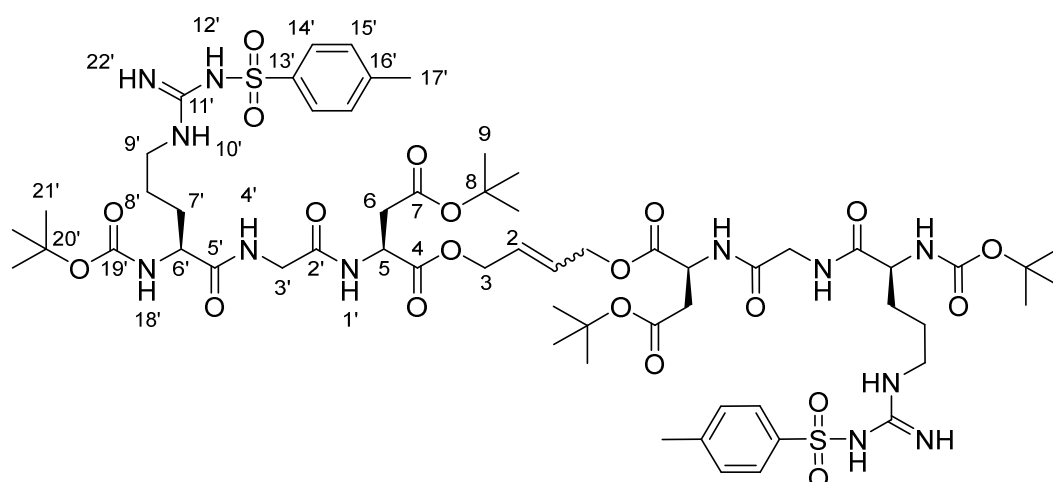
IR (ν, cm⁻¹): 3335, 3010, 2966, 2491, 1749, 1671, 1239, 1181, 822.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 8.2 Hz, 2H, H^{14'}), 7.31 (br s, 2H, NH), 7.24 (d, *J* = 8.2 Hz, 2H, H^{15'}), 7.13 (br s, 1H, H^{1'}), 6.35 (br s, 2H, NH), 5.86 (ddt, *J* = 17.1, 10.5, 5.8 Hz, 1H, H²), 5.45 (d, *J* = 7.8 Hz, 1H, NH), 5.31 (d, *J* = 17.1 Hz, 1H, H^{1trans}), 5.24 (d, *J* = 10.5 Hz, 1H, H^{1cis}), 4.81 (dt, *J* = 7.8, 4.6 Hz, 1H, H⁵), 4.65 (dd, *J* = 12.8, 6.0 Hz, 1H, H^{3a}), 4.59 (dd, *J* = 12.8, 6.0 Hz, 1H, H^{3b}), 4.27 (s, 1H, H⁶), 4.05 (dd, *J* = 16.6, 5.5 Hz, 1H, H^{3a}), 3.92 (dd, *J* = 16.6, 5.5 Hz, 1H, H^{3b}), 3.39-3.18 (m, 2H, H⁹), 2.92 (dd, *J* = 16.7, 4.5 Hz, 1H, H^{6a}), 2.75 (dd, *J* = 16.7, 4.5 Hz, 1H, H^{6b}), 2.40 (s, 3H, H¹⁷), 1.94-1.80 (m, 1H, H^{7a}), 1.73-1.53 (m, 3H, H^{7b} and H⁸), 1.44-1.41 (m, 18H, H⁹ and H²¹).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 170.4 (C⁴ or C⁷ or C^{2'} or C^{5'}), 170.1 (C⁴ or C⁷ or C^{2'} or C^{5'}), 169.0 (C⁴ or C⁷ or C^{2'} or C^{5'}), 166.54 (C⁴ or C⁷ or C^{2'} or C^{5'}), 158.5 (C^{11'} or C^{19'}), 158.5 (C^{11'} or C^{19'}), 141.9 (C^{13'}), 140.8 (C^{16'}), 131.3 (C²), 129.2 (C^{14'}), 126.0 (C^{15'}), 119.0 (C¹), 81.1 (C⁸), 77.2 (C²⁰), 65.9 (C³), 53.6 (C⁶), 48.9 (C⁵), 44.7 (C⁹), 42.9 (C³), 37.2 (C⁶), 30.0 (C⁷), 28.4 (C²¹), 28.0 (C⁹), 25.0 (C⁸), 21.4 (C¹⁷).

HRMS (ESI) – for C₃₁H₄₈N₆NaO₁₀S: 719.3045, found: 719.3013

[α]_D²⁵ +73.1 (*c* = 1.0, CHCl₃).

**3.34****Formula:** C₆₀H₉₂N₁₂O₂₀S₂**Molecular Weight:** 1365.58

To a solution of RGD-allyl **3.35** (600 mg, 0.86 mmol, 1.0 equiv) in 4.3 mL of CH₂Cl₂ was added Hoveyda-Grubbs' second-generation catalyst (27 mg, 0.043 mmol, 0.050 equiv) and the mixture was stirred at reflux for 16 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by column chromatography, (97:3 CH₂Cl₂/MeOH) to give compound **3.34** as a white foam (401 mg, 68%) in an E:Z ratio of 10:1

IR (ν, cm⁻¹): 3335, 3019, 2966, 2491, 1749, 1666, 1239, 1180, 898.

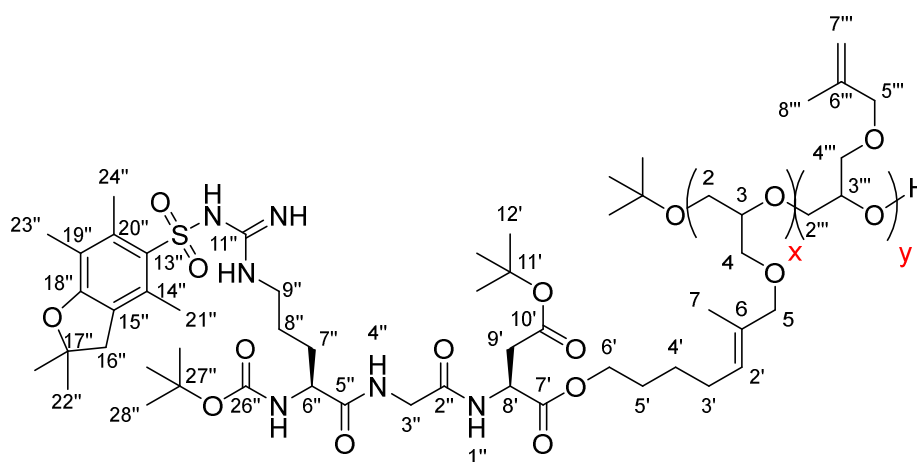
¹H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.1 Hz, 4H, H^{14'}), 7.53 (br s, 4H, NH), 7.21 (d, *J* = 8.1 Hz, 4H, H^{15'}), 6.50 (br s, 4H, NH), 6.36 (br s, 2H, H^{1'}), 5.79 (br s, 2H, NH), 5.77-5.69 (m, 2H, H²), 4.81 (d, *J* = 8.6 Hz, 2H, H⁵), 4.59 (d, *J* = 13.8 Hz, 2H, H^{3a}), 4.52 (d, *J* = 13.8 Hz, 2H, H^{3b}), 4.18 (s, 2H, H⁶), 3.94 (br s, 4H, H³), 3.37-3.05 (m, 4H, H⁹), 2.86-2.68 (m, 4H, H⁶), 2.37 (s, 6H, H¹⁷), 1.90-1.75 (m, 2H, H^{7a}), 1.65-1.50 (m, 6H, H^{7b} and H⁸), 1.47-1.30 (m, 36H, H⁹ and H²¹).

¹³C NMR (101 MHz, CDCl₃) δ ppm: 173.4 (C⁴ or C⁷ or C^{2'} or C^{5'}), 170.4 (C⁴ or C⁷ or C^{2'} or C^{5'}), 169.9 (C⁴ or C⁷ or C^{2'} or C^{5'}), 169.7 (C⁴ or C⁷ or C^{2'} or C^{5'}), 157.1 (C^{11'} or C¹⁹), 156.0 (C^{11'} or C¹⁹), 142.0 (C^{13'}), 140.7 (C^{16'}), 129.2 (C^{14'}), 127.3 (C²), 126.0 (C^{15'}), 81.8 (C⁸), 79.9 (C²⁰), 64.7 (C³), 54.1 (C⁶), 49.0 (C⁵), 43.0 (C⁹), 40.1 (C³), 37.1 (C⁶), 29.5 (C⁷), 28.4 (C^{21'}), 28.0 (C⁹), 25.3 (C⁸), 21.4 (C¹⁷).

HRMS (ESI) – for $\text{C}_{60}\text{H}_{92}\text{N}_{12}\text{NaO}_{20}\text{S}_2$: 1387.5884, found: 1387.5817.

$[\alpha]_{\text{D}}^{25}$ +13.7 ($c = 1.0$, CHCl_3).

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(*tert*-butyl) 1-((*E*)-6-methyl-7-(oxiran-2-ylmethoxy)hept-5-en-1-yl) *N*²-(*tert*-butoxycarbonyl)-*N*^{'''}-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-*L*-arginylglycyl-*L*-aspartate]-*co*-[2-({3-methylbut-3-en-1-yl-oxy}methyl)oxirane]



PMAGE-*graft*-hexenyl-RGD-Boc

Formula: $C_4H_9O(C_{45}H_{72}N_6O_{13}S)_x(C_7H_{12}O_2)_y$

To a solution of PMAGE (50 mg, 0.39 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added RGD-hexenyl **3.44** (327 mg, 0.39 mmol, 1.00 equiv), Hoveyda-Grubbs' second-generation catalyst (12.2 mg, 0.020 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PMAGE-*graft*-hexenyl-RGD-Boc as a brown oil (125 mg, 85%) with an *E:Z* ratio of 3:1.

IR (ν , cm^{-1}): 3330, 3108, 2970, 2363, 1749, 1649, 1505, 1452, 1367, 1232, 1182, 991.

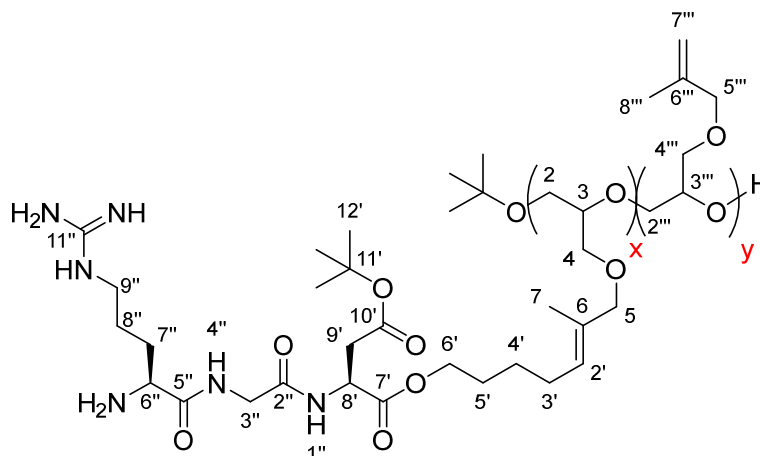
¹H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.17 (s, 9H, CH_3). **Section x**, 7.70 (br s, 1H, $H^{4''}$), 7.36 (br s, 1H, $H^{1''}$), 6.32 (br s, 2H, NH), 6.24-6.11 (m, 2H, NH), 5.72 (br s, 1H, $H^{2'}$), 5.39-5.32 (m, 1H, NH), 4.82 (br s, 1H, H^8), 4.23 (s, 1H, $H^{6''}$), 4.16-4.03 (m, 2H, $H^{6'}$), 4.01-3.92 (m, 2H, H^3), 3.82 (br s, 2H, H^5), 3.76-3.33 (m, 5H, H^{2-4}), 3.26 (br s, 2H, $H^{16''}$), 2.95 (br s, 2H, $H^{9''}$), 2.85 (d, $J = 16.2$ Hz, 1H, $H^{9'a}$), 2.74 (d, $J = 16.2$ Hz, 1H, $H^{9'b}$), 2.57 (s, 3H, $H^{21''}$ or $H^{23''}$ or $H^{24''}$), 2.50 (s, 3H, $H^{21''}$ or $H^{23''}$ or $H^{24''}$), 2.08 (s, 3H, $H^{21''}$ or $H^{23''}$ or $H^{24''}$), 2.05-1.99 (m, 2H, H^3), 1.95-1.81 (m, 1H, $H^{7''a}$), 1.76-1.52 (m, 7H, $H^{7''b}$ & H^8 & $H^{4'}$ & H^5), 1.46 (s, 6H, $H^{22''}$), 1.44-1.39 (m, 18H, $H^{12'}$ and $H^{28''}$). **Section y**, 4.93 (s, 1H, $H^{7'''a}$), 4.85 (s, 1H, $H^{7'''b}$), 3.90-3.84 (m, 2H, $H^{5'''}$), 3.76-3.33 (m, 5H, $H^{2'''-4'''}$), 1.71 (s, 3H, $H^{8'''}$). **Overall Ratio (x;y)** = 31:69 (Average Mw per unit = 380.12 g.mol⁻¹).

¹³C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 173.0 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 170.9 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 169.8 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 169.3 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 158.7 ($C^{11''}$ or $C^{18''}$ or $C^{26''}$), 156.5 ($C^{11''}$ or $C^{18''}$ or $C^{26''}$), 155.9 ($C^{11''}$ or $C^{18''}$ or $C^{26''}$), 138.4 (C^6), 138.3

(ArC), 133.0 (ArC), 132.3 (ArC), 130.4 (C^{2'}), 124.6 (ArC), 117.4 (ArC), 86.3 (C^{17''}), 81.7 (C^{11'}), 79.9* (C³), 78.8* (C³), 77.2 (C^{27'''}), 75.2 (C² or C⁴), 70.2 (C² or C⁴), 69.8 (C⁵), 65.8 (C^{6'}), 53.9 (C^{6''}), 48.9 (C^{8'}), 43.3 (C^{9''}), 43.0 (C^{3''}), 40.4 (C^{16''}), 37.4 (C^{9'}), 32.9 (C^{3'}), 31.8 (C^{7''}), 28.6 (C^{22''} or C^{28''}), 28.4 (C^{22''} or C^{28''}), 28.0 (C^{4'} or C^{5'}), 27.2 (C^{4'} or C^{5'}), 25.7 (C^{8''}), 25.3 (C^{12'}), 19.4 (C^{21''} or C^{23''} or C^{24''}), 18.0 (C^{21''} or C^{23''} or C^{24''}), 13.9 (C⁷), 12.5 (C^{21''} or C^{23''} or C^{24''}). **Section y**, 142.2 (C^{6'''}), 111.9 (C^{7'''}), 79.9* (C^{3'''}), 78.8* (C^{3'''}), 75.2 (C^{2'''} or C^{4'''}), 70.2 (C^{2'''} or C^{4'''}), 70.0 (C^{5'''}), 14.0 (C^{8'''}).

GPC: $M_n = 19576$, $M_w = 21725$, $\bar{D} = 1.10$

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(*tert*-butyl) 1-((*E*)-6-methyl-7-(oxiran-2-ylmethoxy)hept-5-en-1-yl) *L*-arginylglycyl-*L*-aspartate]-co-[2-((3-methylbut-3-en-1-yl-oxy)methyl)oxirane]



PMAGE-*graft*-hexenyl-RGD

Formula: $C_4H_9O(C_{27}H_{48}N_6O_8)_x(C_7H_{12}O_2)_y$

To a solution of PMAGE-*graft*-hexene-RGD-Boc (44 mg, 0.047 mmol, 1.0 equiv) in 2.0 mL of CH_2Cl_2 was added triisopropylsilane (0.1 mL, 0.5 mmol, 10 equiv) and TFA (1.0 mL, 13 mmol, 275 equiv) the mixture was stirred for 2 h at RT. The reaction mixture was then concentrated under vacuum and the product purified by SEC chromatography, LH-20 (1:1 CH_2Cl_2 /MeOH) to give PMAGE-*graft*-hexenyl-RGD as a brown oil (17 mg, 60%) with an *E:Z* ratio of 3:1.

IR (ν , cm^{-1}): 3297, 2970, 2363, 1749, 1649, 1457, 1367, 1232, 1184.

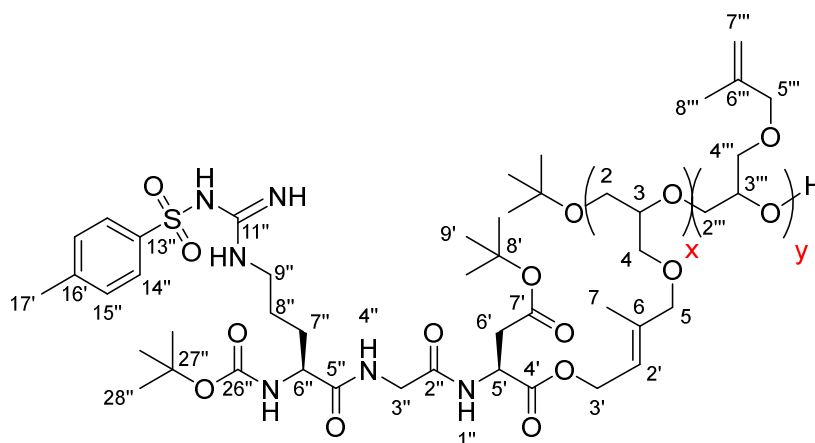
1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.17 (s, 9H, CH_3). **Section x**, 5.43 (t, $J = 5.9$ Hz 1H, $H^{2'}$), 5.37** (t, $J = 5.9$ Hz 1H, $H^{2'}$), 4.65 (br s, 1H, $H^{8'}$), 4.18–4.05 (m, 3H, $H^{6'}$ and $H^{6''}$), 4.03–3.95 (m, 2H, $H^{3''}$), 3.88 (br s, 2H, H^5), 3.80–3.38 (m, 5H, H^{2-4}), 3.26–3.18 (m, 2H, $H^{9''}$), 2.86 (d, $J = 16.6$ Hz, 1H, $H^{9'a}$), 2.54 (d, $J = 16.6$ Hz, 1H, $H^{9'b}$), 2.13–2.04 (m, 2H, $H^{3'}$), 1.91–1.80 (m, 1H, $H^{7'a}$), 1.65 (s, 3H, H^7), 1.58–1.51 (m, 1H, $H^{7'b}$), 1.49–1.31 (m, 6H, $H^{4'}$ and $H^{5'}$ and $H^{8''}$), 1.20 (s, 9H, $H^{12'}$). **Section y**, 4.98 (s, 1H, $H^{7''a}$), 4.89 (s, 1H, $H^{7''b}$), 3.92 (br s, 2H, $H^{5''}$), 3.80–3.38 (m, 5H, $H^{2''-4''}$), 1.74 (s, 3H, $H^{8''}$). **Overall Ratio (x;y)** = 30:70 (Average Mw per unit = 264.8 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 172.6 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 170.0 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 169.1 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 160.0 ($C^{7'}$ or $C^{10'}$ or $C^{2''}$ or $C^{5''}$), 158.0 ($C^{11''}$), 134.0 (C^6), 130.3 ($C^{2'}$), 128.9** ($C^{2'}$), 81.2 ($C^{11'}$), 80.2* (C^3), 79.5* (C^3), 76.3 (C^2 or C^4), 71.3 (C^2 or C^4), 69.9 (C^5), 66.3 (C^6), 58.6 ($C^{6''}$), 50.8 (C^8), 40.9 ($C^{9''}$), 40.1 ($C^{3''}$), 37.4 (C^9), 32.9 (C^3), 31.8 ($C^{7''}$), 28.3 ($C^{4'}$ or $C^{5'}$), 27.2 ($C^{4'}$ or $C^{5'}$), 27.0 ($C^{8''}$), 20.0 ($C^{12'}$), 14.0 (C^7). **Section y**, 143.7 ($C^{6''}$), 112.7 ($C^{7''}$), 80.2* ($C^{3''}$), 79.5* ($C^{3''}$), 76.3 ($C^{2''}$ or $C^{4''}$), 71.3 ($C^{2''}$ or $C^{4''}$), 70.0 ($C^{5''}$), 14.4 ($C^{8''}$).

****Z isomer**

GPC: $M_n = 18790$, $M_w = 20796$, $\bar{D} = 1.11$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[4-(*tert*-butyl) 1-((*E*)-3-methyl-4-(oxiran-2-ylmethoxy)but-2-en-1-yl) *N*²-(*tert*-butoxycarbonyl)-*N*^ω-tosyl-*L*-arginylglycyl-*L*-aspartate]-co-[2-({3-methylbut-3-en-1-yl-oxy}methyl)oxirane]



PMAGE-*graft-allyl-RGD-Boc*

Formula: $C_4H_9O(C_{36}H_{58}N_6O_{12}S)_x(C_7H_{12}O_2)_y$

To a solution of PMAGE (50 mg, 0.39 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 was added RGD-allyl **3.34** (272 mg, 0.39 mmol, 1.00 equiv), Hoveyda-Grubbs' second-generation catalyst (12.2 mg, 0.020 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture was then concentrated under vacuum and the product purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PMAGE-*graft-allyl-RGD-Boc* as a brown oil (47 mg, 75%) with an *E:Z* ratio of 3:1.

IR (ν , cm^{-1}): 2907, 2864, 1651, 1087, 921.

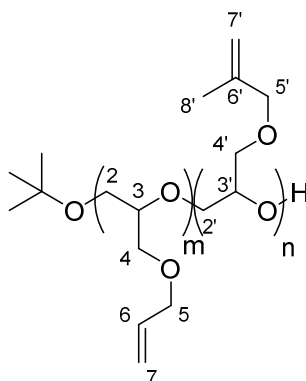
¹H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.17 (s, 9H, CH_3). **Section x**, mostly unobservable, except; 7.82-7.78 (m, 2H, $H^{14''}$), 7.26-7.22 (m, 2H, $H^{13''}$), 5.35-5.30 (m, 1H, H^2), 3.77-3.36 (m, 5H, H^{2-4}), 3.22-3.18 (br s, 2H, H^6), 2.89-2.85 (m, 1H, $H^{9''a}$), 2.82-2.79 (m, 1H, $H^{9''b}$), 1.49-1.39 (m, 18H, $H^{9'}$ and $H^{28''}$). **Section y**, 4.93 (s, 1H, $H^{7'''a}$), 4.85 (s, 1H, $H^{7'''b}$), 3.89 (br s, 2H, $H^{5'''}$), 3.77-3.36 (m, 5H, $H^{2'''-4'''}$), 1.73 (s, 3H, $H^{8'''}$). **Overall Ratio (x;y)** = 5:95 (Average Mw per unit = 161.40 g.mol⁻¹).

¹³C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, mostly unobservable except polymer backbone; 79.0* (C^3), 78.8* (C^3), 75.2 (C^2 or C^4), 70.2 (C^2 or C^4), 70.0 (C^5), **Section y**, 142.2 ($C^{6'''}$), 111.9 ($C^{7'''}$), 79.0* ($C^{3'''}$), 78.8* ($C^{3'''}$), 75.2 ($C^{2'''}$ or $C^{4'''}$), 70.2 ($C^{2'''}$ or $C^{4'''}$), 70.0 ($C^{5'''}$), 19.4 ($C^{8'''}$).

*diastereomers

GPC: M_n = 10823, M_w = 12540, \bar{D} = 1.16.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({allyloxy}methyl)oxirane]-*co*-[2-({2-Methallyloxy}methyl)oxirane]



PAGE-*co*-PMAGE

Formula: $C_4H_9O(C_6H_{10}O_2)_m(C_7H_{12}O_2)_n$

To a 1 M solution of potassium *tert*-butoxide in THF (0.18 mL, 0.175 mmol, 1.0 equiv) was added a degassed mixture of allyl glycidyl ether (2.00 g, 17.5 mmol, 100 equiv) and methallyl glycidyl ether (2.25 g, 17.5 mmol, 100 equiv) at 2 mL/hour for 4 h. The reaction mixture was stirred at 45 °C for 20 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomers were distilled off to afford PAGE-*co*-PMAGE (4.20 g, 99% brsm) as a yellow oil.

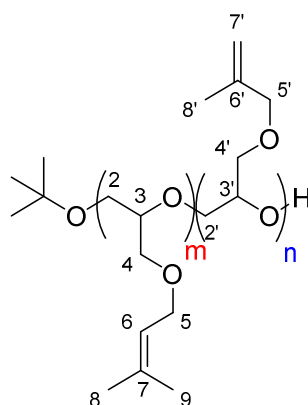
IR (ν , cm^{-1}): 2910, 2864, 1654, 1089, 920, 889.

1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.18 (s, 9H, CH_3), **Section m**, 5.89 (ddt, J = 17.3, 10.8, 5.5 Hz, 1H, H^6), 5.27 (dd, J = 17.3, 1.5 Hz, 1H, H^{7trans}), 5.17 (dd, J = 10.8, 1.5 Hz, 1H, H^{7cis}), 3.99 (d, J = 5.5 Hz, 2H, H^5), 3.75–3.32 (m, 5H, H^{2-4}). **Section n**, 4.95 (s, 1H, $H^{7'a}$), 4.87 (s, 1H, $H^{7'b}$), 3.88 (s, 2H, $H^{5'}$), 3.75–3.32 (m, 5H, $H^{2'-4'}$), 1.72 (s, 3H, H^8).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: **Section m**, 134.9 (C^6), 116.7 (C^7), 78.9 (C^3), 72.3 (C^5), 72.2, 70.2, 69.9 (C^2 & C^4). **Section n**, 142.2 ($C^{6'}$), 111.9 ($C^{7'}$), 78.9 ($C^{3'}$), 75.2 ($C^{5'}$), 72.2, 70.2, 69.9 ($C^{2'}$ & $C^{4'}$), 19.4 (C^8).

GPC: M_n = 12505, M_w = 16665, \bar{D} = 1.33.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({3-Methylbut-2-en-1-yl-oxy}methyl)oxirane]-*co*-[2-({2-Methallyloxy}methyl)oxirane]



PPGE-*co*-PMAGE

Formula: $C_4H_9O(C_8H_{14}O_2)_m(C_7H_{12}O_2)_n$

To a 1 M solution of potassium *tert*-butoxide in THF (0.12 mL, 0.11 mmol, 1.0 equiv) was added a degassed mixture of prenyl glycidyl ether (1.50 g, 10.6 mmol, 100 equiv) and methyl allyl glycidyl ether (1.35 g, 10.6 mmol, 100 equiv) at 1 mL/hour for 3 h. The reaction mixture was stirred at 45 °C for 20 h. The reaction mixture was quenched with methanol (0.10 mL, 2.4 mmol) and stirred for 1 h. Residual monomers were distilled off to afford PPGE-*co*-PMAGE (2.80 g, 95% brsm) as a yellow oil.

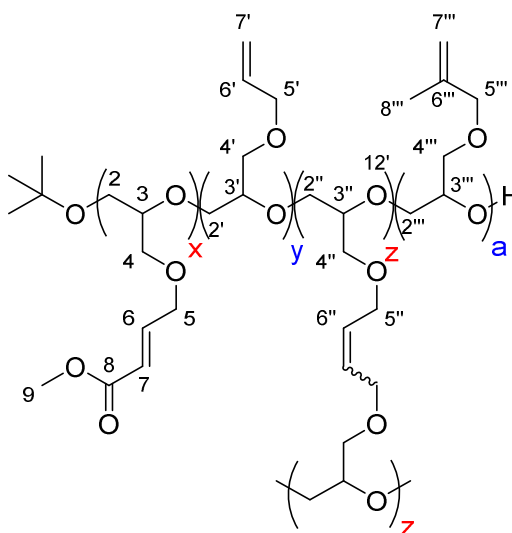
IR (ν , cm^{-1}): 2910, 2865, 1670, 1099, 899

^1H NMR (400 MHz, CDCl_3) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3), **Section x**, 5.34 (t, $J = 6.7$ Hz, 1H, H^6), 3.98 (d, $J = 6.7$ Hz, 2H, H^5), 3.67–3.39 (m, 5H, H^{2-4}), 1.72 (s, 3H, H^8 or H^9), 1.67 (s, 3H, H^8 or H^9). **Section y**, 4.96 (s, 1H, H^{7a}), 4.88 (s, 1H, H^{7b}), 3.88 (s, 2H, H^5), 3.67–3.39 (m, 5H, H^{2-4}), 1.75 (s, 3H, H^8).

^{13}C NMR (101 MHz, CDCl_3) δ ppm: **Section x**: 136.3 (C^7), 121.5 (C^6), 78.8 (C^3), 70.1, 69.8, 67.8 (C^2 & C^4), 25.8 (C^7 or C^8), 18.1 (C^7 or C^8). **Section y**: 142.3 (C^6), 111.9 (C^7), 78.8 (C^3), 75.2 (C^5), 70.1, 69.8, 67.8 (C^2 & C^4), 19.4 (C^8).

GPC: $M_n = 12480$, $M_w = 13870$, $D = 1.18$

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl 4-(oxiran-2-ylmethoxy)but-2-enoate]-co-[2-({allyl oxy}methyl)oxirane]-co-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]-co-[2-({2-Methallyloxy}methyl)oxirane]



PAGE-co-PMAGE-graft-MA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z(C_7H_{12}O_2)_a$

To a solution of PAGE-co-PMAGE (54:46) (53 mg, 0.44 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added methyl acrylate (0.16 mL, 1.8 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.02 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-co-PMAGE-graft-MA as a brown oil (51 mg, 90%).

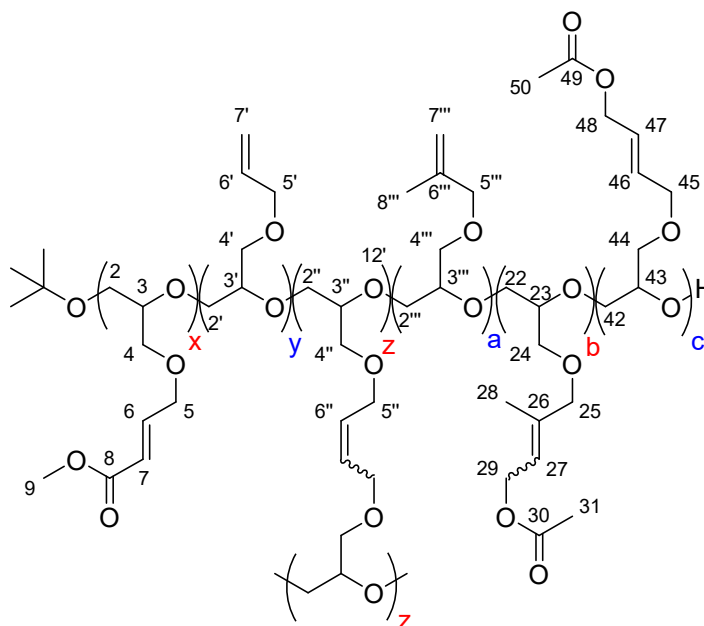
IR (ν , cm^{-1}): 2875, 1722, 1668, 1255, 1066, 880.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.93 (dt, J = 15.8, 4.1 Hz, 1H, H^6), 6.07 (d, J = 15.7 Hz, 1H, H^7), 4.16 (br s, 2H, H^5), 3.97–3.31 (m, 8H, $H^{2-4 \& 9}$). **Section y**, 5.77 (br s, 1H, H^6), 5.59–5.42 (m, 2H, H^7), 4.05–3.95 (m, 2H, H^5), 3.97–3.31 (m, 5H, $H^{2'-4'}$). **Section z**, 5.95–5.91 (m, 1H, $H^{6''}$), 4.05–3.95 (m, 2H, $H^{5''}$), 3.97–3.31 (m, 5H, $H^{2''-4''}$). **Section a**, 4.94 (s, 1H, $H^{7a'''}$), 4.87 (s, 1H, $H^{7b'''}$), 3.88 (s, 2H, $H^{5'''}$), 3.97–3.31 (m, 5H, $H^{2'''-4'''}$), 1.71 (s, 3H, $H^{8'''}$). **Overall Ratio (x;y;z:a)** = 18:12:18:52 (Average Mw per unit = 129.30 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 166.9 (C^8), 144.9 (C^6), 120.8 (C^7), 79.4* (C^3), 78.9* (C^3), 70.4, 72.9, 69.9, 69.4 (C^2 & C^4 & C^5), 51.5 (C^9). **Section y**, 128.2 (C^6), 116.7 (C^7), 79.4* (C^3), 78.9* (C^3), 70.4, 72.9, 69.9, 69.4 ($C^{2'}$ & $C^{4'}$ & $C^{5'}$). **Section z**, 128.5 ($C^{6''}$), 79.4* ($C^{3''}$), 78.9* ($C^{3''}$), 70.4, 72.9, 69.9, 69.4 ($C^{2''}$ & $C^{4''}$ & $C^{5''}$). **Section a**, 142.2 ($H^{6'''}$), 111.9 ($H^{7'''}$), 79.4* ($C^{3'''}$), 78.9* ($C^{3'''}$), 72.9, 70.4, 72.9, 69.9, 69.4 ($C^{2'''}&C^{4'''}&C^{5'''}&C^{5'''}&C^{5'''}&C^{5'''}$), 19.5 ($H^{8'''}$).

GPC: $M_n = 13270$, $M_w = 23223$, $D = 1.75$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl-4-(oxiran-2-ylmethoxy)but-2-enoate]-co-[2-({allyloxy}methyl)oxirane]-co-[1,4-*bis*(oxiran-2-ylmethoxy)but-2-ene]-co-[2-({2-Methallyloxy}methyl)oxirane]-co-[(*E*)-3-methyl-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-co-[(*E*)-4-(oxiran-2-ylmethoxy)but-2-en-1-yl-acetate]-co-[2-({allyloxy}methyl)oxirane]



PAGE-co-PMAGE-graft-MA-graft-AA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_6H_{10}O_2)_y(C_{10}H_{16}O_4)_z(C_7H_{12}O_2)_a(C_{10}H_{16}O_4)_b(C_9H_{14}O_4)_c$

To a solution of PAGE-co-PMAGE-graft-MA (51 mg, 0.21 mmol, 1.0 equiv, w.r.t PMAGE) in 1.1 mL of CH_2Cl_2 was added allyl acetate **2.3** (140 mg, 0.84 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (6.3 mg, 0.01 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-co-PMAGE-graft-MA-graft-AA as a brown oil (52 mg, 80%).

IR (ν , cm^{-1}): 2873, 1722, 1666, 1254, 1066, 910.

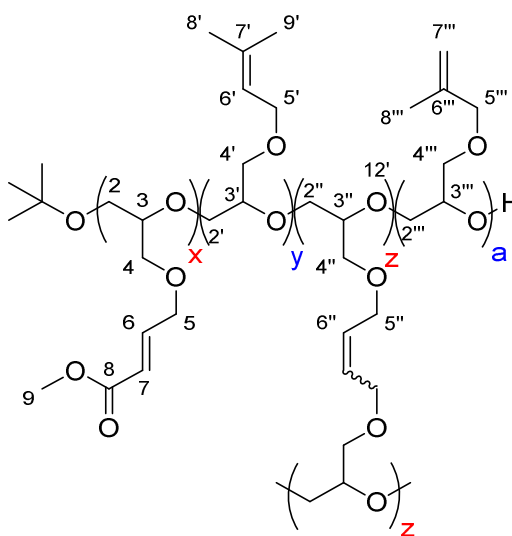
1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.92 (dt, $J = 15.7, 4.3$ Hz, 1H, H^6), 6.06 (d, $J = 15.8$ Hz, 1H, H^7), 4.18–4.12 (m, 2H, H^5), 3.80–3.32 (m, 8H, $H^{2-4 \text{ \& } 9}$). **Section y**, 5.87–5.69 (m, 1H, $H^{6'}$), 5.24 (d, $J = 17.1$ Hz, 1H, $H^{7a'}$), 5.14 (d, $J = 10.2$ Hz, 1H, $H^{7b'}$), 4.01–3.95 (m, 2H, H^5), 3.80–3.32 (m, 5H, $H^{2'-4'}$). **Section z**, 5.87–5.69 (m, 1H, $H^{6''}$), 4.01–3.95 (m, 2H, H^5), 3.80–3.32 (m, 5H, $H^{2''-4''}$). **Section a**, 4.93 (s, 1H, $H^{7a''}$), 4.85 (s, 1H, $H^{7b''}$), 3.86 (s, 2H, $H^{5''}$), 3.80–3.32 (m, 5H, $H^{2'''-4'''}$), 1.70 (s, 3H, $H^{8''}$). **Section b**, 5.68–5.50 (m, 1H, H^{27}), 4.61 (d, $J = 6.7$ Hz, 2H, H^{29}), 4.01–3.95 (m, 2H, H^{25}), 3.80–3.32 (m,

5H, H²²⁻²⁴), 2.04 (s, 3H, H²⁸), 1.70 (s, 3H, H³¹). **Section c**, 5.87–5.69 (m, 2H, H⁴⁶ & H⁴⁷), 4.54 (d, $J = 4.6$ Hz, 2H, H⁴⁸), 4.01–3.95 (m, 2H, H⁴⁵), 3.80–3.32 (m, 5H, H⁴²⁻⁴⁴), 2.04 (s, 3H, H⁵⁰). **Overall Ratio (x;y;z:a:[b+c])** = 19:4:10:51:15 (Average Mw per unit = 161.10 g.mol⁻¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: **Initiator**, not observed. **Section x**, 166.6 (C⁸), 144.8 (C⁶), 120.8 (C⁷), 79.9* (C³), 78.8* (C³), 78.6* (C³), 72.2, 71.0, 70.1, 69.9, 69.4, 66.9 (C² & C⁴ & C⁵), 51.5 (C⁹). **Section y**, 129.2 (C^{6'} or C^{6''}), 128.0 (C^{6'} or C^{6''}), 118.9 (C^{7'}), 79.9* (C^{3'}), 78.8* (C^{3'}), 78.6* (C^{3'}), 72.2, 71.0, 70.1, 69.9, 69.4, 66.9 (C^{2'} & C^{4'} & C^{5'}). **Section z**, 129.2 (C^{6'} or C^{6''}), 128.0 (C^{6'} or C^{6''}), 79.9* (C^{3''}), 78.8* (C^{3''}), 78.6* (C^{3''}), 72.2, 71.0, 70.1, 69.9, 69.4, 66.9 (C^{2''} & C^{4''} & C^{5''}). **Section a**, 142.2 (H^{6'''}), 111.9 (H^{7'''}), 79.9* (C^{3'''}), 78.8* (C^{3'''}), 78.6* (C^{3'''}), 72.2, 71.0, 70.1, 69.9, 69.4, 66.9 (C^{2'''} & C^{4'''} & C^{5'''}), 19.5 (H^{8'''}). **Section b**, 170.6 (C³⁰), 142.2 (C²⁶), 120.6 (C²⁷), 79.9* (C²³), 78.8* (C²³), 78.6* (C²³), 75.8 (C²⁵), 72.2, 71.0, 70.1, 69.9, 69.4, 66.9 (C²² & C²⁴ & C²⁵), 60.2 (C²⁹), 20.9 (C³¹), 19.4 (C²⁸). **Section c**, 170.6 (C⁴⁹), 131.1 (C⁴⁶), 126.2 (C⁴⁷), 79.9* (C⁴³), 78.8* (C⁴³), 78.6* (C⁴³), 72.2, 71.0, 70.1, 69.9, 69.4, 66.9 (C⁴² & C⁴⁴ & C⁴⁵), 64.3 (C⁴⁸), 20.9 (C⁵⁰).

GPC: $M_n = 14891$, $M_w = 22845$, $\bar{D} = 1.53$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl 4-(oxiran-2-ylmethoxy)but-2-enoate]-co-[2-({3-Methylbut-2-en-1-yl-oxy}methyl)oxirane]-co-[1,4-bis(oxiran-2-ylmethoxy)but-2-ene]-co-[2-({2-Methallyloxy}methyl)oxirane]



PPGE-co-PMAGE-*graft*-MA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_8H_{14}O_2)_y(C_{10}H_{16}O_4)_z(C_7H_{12}O_2)_a$

To a solution of PPGE-co-PMAGE (50:50) (60 mg, 0.44 mmol, 1.0 equiv) in 1.1 mL of CH_2Cl_2 was added methyl acrylate (0.16 mL, 1.8 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (14 mg, 0.02 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing the product PPGE-co-PMAGE-*graft*-MA as a brown oil (52 mg, 85%).

IR (ν , cm^{-1}): 2942, 1737, 1737, 1228, 1026.

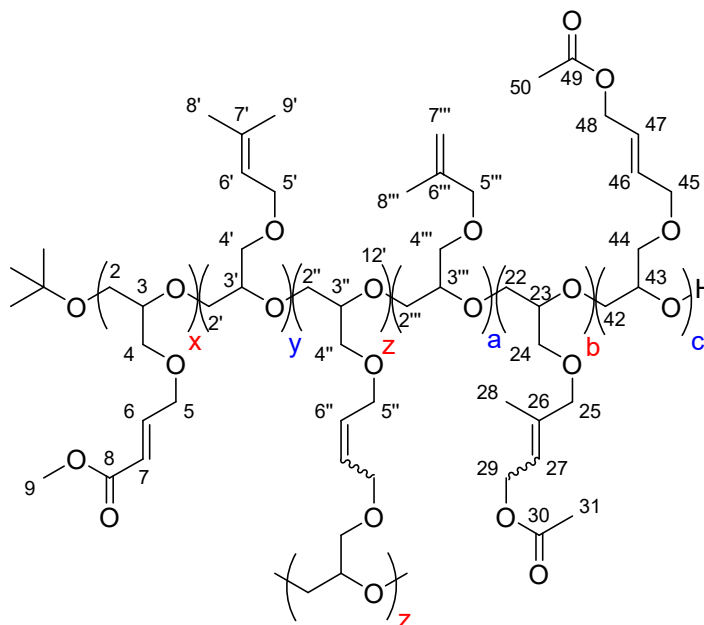
1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.92 (dt, $J = 15.8, 4.5$ Hz, 1H, H^6), 6.05 (d, $J = 15.8$ Hz, 1H, H^7), 4.18–4.14 (m, 2H, H^5), 3.99–3.41 (m, 8H, H^{2-4} & 9). **Section y**, 5.35–5.29 (m, 1H, H^6), 4.05–3.95 (m, 2H, H^5), 3.99–3.41 (m, 5H, $H^{2'-4'}$), 1.75 (s, 3H, $H^{8'}$ or $H^{9'}$), 1.67 (s, 3H, $H^{8'}$ or $H^{9'}$). **Section z**, 5.35–5.29 (m, 1H, H^6), 4.05–3.95 (m, 2H, H^5), 3.99–3.41 (m, 5H, $H^{2''-4''}$). **Section a**, 4.93 (s, 1H, $H^{7a''}$), 4.85 (s, 1H, $H^{7b''}$), 3.88 (s, 2H, $H^{5''}$), 3.99–3.41 (m, 5H, $H^{2'''-4'''}$), 1.71 (s, 3H, $H^{8''}$). **Overall Ratio (x;y;z:a)** = 18:12:18:52 (Average Mw per unit = 139.90 g.mol $^{-1}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section x**, 166.6 (C^8), 144.7 (C^6), 120.6 (C^7), 78.9* (C^3), 78.8* (C^3), 77.7, 75.2, 72.9, 70.2, 70.0, 69.4 (C^2 & C^4 & C^5), 51.5 (C^9). **Section y**, 137.3 (C^7), 121.8 (C^6), 78.9* (C^3), 78.8* (C^3), 77.7, 75.2, 72.9, 70.2, 70.0, 69.4 ($C^{2'}$ & $C^{4'}$ & C^5), 25.8 ($C^{8'}$ or $C^{9'}$), 15.7 ($C^{8'}$ or $C^{9'}$). **Section z**, 128.5 (C^6), 78.9*

(C^{3''}), 78.8* (C^{3''}), 77.7, 75.2, 72.9, 70.2, 70.0, 69.4 (C^{2''} & C^{4''} & C^{5''}). **Section a**, 142.2 (H^{6'''}), 111.9 (H^{7'''}), 78.9* (C^{3'''}), 78.8* (C^{3'''}), 77.7, 75.2, 72.9, 70.2, 70.0, 69.4 (C^{2'''} & C^{4'''} & C^{5'''}), 19.4 (H^{8'''}).

GPC: $M_n = 23749$, $M_w = 44716$, $\bar{D} = 1.88$.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[methyl 4-(oxiran-2-ylmethoxy)but-2-enoate]-co-[2-({allyloxy}methyl)oxirane]-co-[2-({3-Methylbut-2-en-1-yl-oxy}methyl)oxirane]-co-[2-({2-Methallyloxy}methyl)oxirane]-co-[(*E*)-3-methyl-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-co-[(*E*)-4-(oxiran-2-ylmethoxy)but-2-en-1-yl acetate]-co-[2-({allyloxy}methyl)oxirane]



PPGE-co-PMAGE-graft-MA-graft-AA

Formula: $C_4H_9O(C_8H_{12}O_4)_x(C_8H_{14}O_2)_y(C_{10}H_{16}O_4)_z(C_7H_{12}O_2)_a(C_{10}H_{16}O_4)_b(C_9H_{14}O_4)_c$

To a solution of PPGE-co-PMAGE-graft-MA (52 mg, 0.19 mmol, 1.0 equiv, w.r.t. PMAGE) in 1.1 mL of CH_2Cl_2 was added allyl acetate **2.3** (130 mg, 0.76 mmol, 4.0 equiv), Hoveyda-Grubbs' second-generation catalyst (6 mg, 0.01 mmol, 0.05 equiv) and the mixture was stirred at reflux for 18 h. The reaction mixture was quenched with dimethyl sulfoxide (0.1 mL, 1.4 mmol) and stirred for 5 min. The reaction mixture directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PPGE-co-PMAGE-graft-MA-graft-AA as a brown oil (51 mg, 90%).

IR (ν , cm^{-1}): 3365, 2881, 1720, 1666, 1255, 1066, 921.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 6.92 (d, $J = 15.8$ Hz, 1H, H^6), 6.06 (d, $J = 15.8$ Hz, 1H, H^7), 4.18–4.11 (m, 2H, H^5), 3.77–3.36 (m, 8H, H^{2-4} & 9). **Section y**, 5.23–5.21 (m, 1H, H^6), 4.04–3.95 (m, 2H, H^5), 3.77–3.36 (m, 5H, $H^{2'-4'}$), 1.74 (s, 3H, $H^{8'}$ or $H^{9'}$), 1.66 (s, 3H, $H^{8'}$ or $H^{9'}$). **Section z**, 5.88–5.71 (m, 1H, $H^{6''}$), 4.04–3.95 (m, 2H, $H^{5''}$), 3.77–3.36 (m, 5H, $H^{2''-4''}$). **Section a**, 4.93 (s, 1H, $H^{7a'''}$), 4.85 (s, 1H, $H^{7b'''}$), 3.86 (s, 2H, $H^{5'''}$), 3.77–3.36 (m, 5H, $H^{2'''-4'''}$), 1.70 (s, 3H, $H^{8'''}$). **Section b**, 5.56 (t, $J = 7.1$ Hz, 1H, H^{27}), 4.61 (d, $J = 6.7$ Hz, 2H, H^{29}), 4.18–4.11 (m, 2H, H^{25}), 3.77–3.36 (m, 5H, H^{22-24}), 2.09–1.99 (m, 3H, H^{28}), 1.70 (s, 3H, H^{31}). **Section c**, 5.88–5.71 (m, 2H, H^{46} & H^{47}), 4.54 (d, $J =$

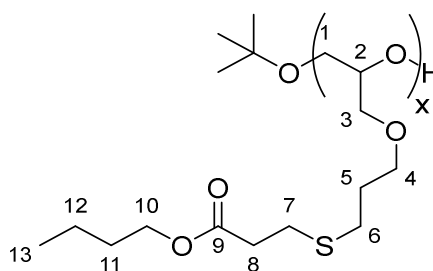
4.5 Hz, 2H, H⁴⁸), 4.18-4.11 (m, 2H, H⁴⁵), 3.77–3.36 (m, 5H, H⁴²⁻⁴⁴), 2.09-1.99 (m, 3H, H⁵⁰).

Overall Ratio (x;y;z:a:[b+c]) = 24:3:3:44:26 (Average Mw per unit = 163.06 g.mol⁻¹).

¹³C NMR (126 MHz, CDCl₃) δ ppm: **Initiator**, not observed. **Section x**, 166.6 (C⁸), 144.8 (C⁶), 120.6 (C⁷), 78.9* (C³), 78.8* (C³), 78.7* (C³), 76.1, 72.2, 71.0, 70.2, 69.9, 69.4, 66.9 (C² & C⁴ & C⁵), 51.5 (C⁹). **Section y**, 137.2 (C⁷), 121.2 (C⁶), 78.9* (C³'), 78.8* (C³'), 78.7* (C³'), 76.1, 72.2, 71.0, 70.2, 69.9, 69.4, 66.9 (C²' & C⁴' & C⁵'), 25.8 (C⁸' or C⁹'), 14.0 (C⁸' or C⁹'). **Section z**, 126.2 (C⁶'' or C⁶''), 78.9* (C³''), 78.8* (C³''), 78.6* (C³''), 76.1, 72.2, 71.0, 70.2, 69.9, 69.4, 66.9 (C²'' & C⁴'' & C⁵''). **Section a**, 142.2 (H^{6'''}), 111.9 (H^{7'''}), 78.9* (C^{3'''}), 78.8* (C^{3'''}), 78.6* (C^{3'''}), 76.1, 72.2, 71.0, 70.2, 69.9, 69.4, 66.9 (C^{2'''} & C^{4'''} & C^{5'''}), 19.4 (H^{8'''}). **Section b**, 170.9 (C³⁰ or C⁴⁹), 170.6 (C³⁰), 142.2 (C²⁶), 120.6 (C²⁷), 78.9* (C²³), 78.8* (C²³), 78.6* (C²³), 76.1, 72.2, 71.0, 70.2, 69.9, 69.4, 66.9 (C²² & C²⁴ & C²⁵), 60.3 (C²⁹), 20.9 (C³¹), 19.4 (C²⁸). **Section c**, 170.9 (C³⁰ or C⁴⁹), 170.6 (C⁴⁹), 131.1 (C⁴⁶), 126.2 (C⁴⁷), 78.9* (C⁴³), 78.8* (C⁴³), 78.6* (C⁴³), 76.1, 72.2, 71.0, 70.2, 69.9, 69.4, 66.9 (C⁴² & C⁴⁴ & C⁴⁵), 64.3 (C⁴⁸), 20.9 (C⁵⁰).

GPC: Mn = 22453, Mw = 38213, Đ = 1.70.

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[butyl 3-((3-(oxiran-2-ylmethoxy)propyl)thio)propanoate]



PAGE-*graft*-BMP

Formula: $C_4H_9O(C_{13}H_{24}O_4S)_x$

To a solution of PAGE (50 mg, 0.44 mmol, 1.0 equiv) in 1.0 mL of toluene was added butyl 3-mercaptopropionate (350 μ L, 2.2 mmol, 5.0 equiv) and AIBN (36 mg, 0.22 mmol, 0.5 equiv). The reaction mixture was degassed *via* three freeze-pump-thaw cycles and heated at 80 $^{\circ}$ C for 18 h. The reaction mixture was quenched with methanol (1.0 mL, 24 mmol) and stirred for 5 min. The reaction mixture was directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PAGE-*graft*-BMP as a clear oil (118 mg, 97%).

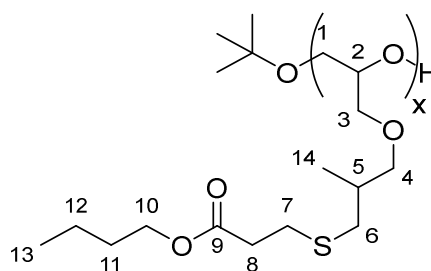
IR (ν , cm^{-1}): 2992, 1740, 1121, 1083, 955

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 4.09 (t, J = 6.7 Hz, 2H, H^{10}), 3.66–3.32 (m, 7H, H^{1-4}), 2.76 (t, J = 7.4 Hz, 2H, H^8), 2.61–2.56 (m, 4H, $H^{6\&7}$), 1.87–1.78 (m, 2H, H^5), 1.65–1.56 (m, 2H, H^{11}), 1.44–1.32 (m, 2H, H^{12}), 0.93 (t, J = 7.4 Hz, 3H, H^{13}).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 171.9 (C^9), 78.6* (C^2), 77.2* (C^2), 71.0, 70.9, 70.0 (C^1 & C^3 & C^4), 64.5 (C^{10}), 39.6 (C^8), 35.2 (C^6 or C^7), 34.9 (C^6 or C^7), 30.6 (C^{11}), 29.6 (C^5), 19.1 (C^{12}), 13.7 (C^{13}).

GPC: M_n = 15377, M_w = 17683, \bar{D} = 1.15

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[butyl 3-((3-(oxiran-2-ylmethoxy)propyl)thio)propanoate]



PMAGE-*graft*-BMP

Formula: $C_4H_9O(C_{14}H_{26}O_4S)_x$

To a solution of PMAGE (56 mg, 0.44 mmol, 1.0 equiv) in 1.0 mL of toluene was added butyl 3-mercaptopropionate (350 μ L, 2.2 mmol, 5.0 equiv) and AIBN (36 mg, 0.22 mmol, 0.5 equiv). The reaction mixture was degassed *via* three freeze-pump-thaw cycles and heated at 80 $^{\circ}$ C for 18 h. The reaction mixture was quenched with methanol (1.0 mL, 24 mmol) and stirred for 5 min. The reaction mixture was directly purified by size exclusion chromatography, LH-20 (1:1 MeOH/ CH_2Cl_2) furnishing PMAGE-*graft*-BMP as a clear oil (120 mg, 95%).

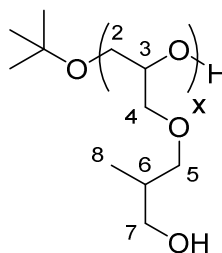
IR (ν , cm^{-1}): 3010, 1745, 1196, 1110, 920.

1H NMR (500 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section x**, 4.10 (t, J = 6.7 Hz, 2H, H^{10}), 3.71–3.23 (m, 7H, H^{1-4}), 2.76 (t, J = 7.4 Hz, 2H, H^8), 2.64–2.57 (m, 4H, $H^{6\&7}$), 2.42–2.38 (m, 1H, H^5), 1.69–1.58 (m, 2H, H^{11}), 1.44–1.34 (m, 2H, H^{12}), 1.01 (d, J = 7.0 Hz, 3H, H^{14}), 0.94 (t, J = 7.4 Hz, 3H, H^{13}).

^{13}C NMR (126 MHz, $CDCl_3$) δ ppm: **Section x**, 171.9 (C^9), 78.6 (C^2), 71.3, 70.1, 69.8 (C^1 & C^3 & C^4), 64.9 (C^{10}), 36.3 (C^8), 35.1 (C^6 or C^7), 34.9 (C^6 or C^7), 34.0 (C^5), 30.6 (C^{11}), 19.1 (C^{12}), 16.8 (C^{14}), 13.7 (C^{13}).

GPC: M_n = 23560, M_w = 26622, \bar{D} = 1.13

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-({proan-3-ol}methyl)oxirane]



PMAGE-OH

Formula: $C_4H_9O(C_7H_{14}O_3)_x$

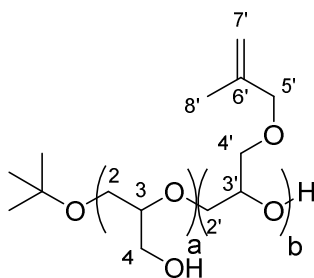
To a solution of PMAGE (100 mg, 0.78 mmol, 1.0 equiv) in 3.0 mL of THF was added $BH_3 \cdot DMS$ (65 mg, 0.86 mmol, 1.1 equiv) dropwise at 0 °C and the mixture was stirred for 2 h. To the reaction mixture was added aqueous 3 N aqueous NaOH (1.13 mL, 3.38 mmol, 4.5 equiv) and aqueous 30% w/w H_2O_2 (240 μ L, 2.34 mmol, 3.0 equiv), and the reaction mixture was left to stir at RT for 1 h. THF was removed under vacuum and the crude mixture purified using size exclusion chromatography, LH-20 (MeOH) furnishing PMAGE-OH as a clear oil (76 mg, 67%).

IR (ν , cm^{-1}): 3330, 3022, 2906, 2865, 1090.

1H NMR (400 MHz, Methanol- d_4) δ ppm: **Initiator**, 1.16 (s, 9H, CH_3). **Section x**, 3.93–3.04 (m, 9H, $H^{2-5\&7}$), 2.04–1.64 (m, 1H, H^6), 0.95–0.90 (m, 3H, H^8).

^{13}C NMR (101 MHz, Methanol- d_4) δ ppm: **Initiator**, not observed. **Section x**, 78.7* (C^3), 78.1* (C^3), 73.8, 70.9, 69.9, 69.7, 64.3 (C^2 & C^4 & C^5 & C^7), 36.1 (C^6), 13.2 (C^8).

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[oxiran-2-ylmethanol]-*co*-[2-({2-Methallyl oxy}methyl)oxirane]



PG-*co*-PMAGE

Formula: $C_4H_9O(C_3H_6O_2)_x(C_7H_{12}O_2)_y$

To a solution of PAGE-*co*-MAGE (1:1) (200 mg, 0.82 mmol, 1.0 equiv) in 1.2 mL of MeOH was added 1,3-dimethylbarbituric acid (258 mg, 1.65 mmol, 2.00 equiv) and $Pd(PPh_3)_4$ (48 mg, 0.04 mmol, 0.05 equiv) and the mixture was stirred for at RT for 18 h. The crude mixture was purified using size exclusion chromatography, LH-20 (MeOH/ CH_2Cl_2 2:1) furnishing PG-*co*-PMAGE as a yellow oil (160 mg, 97%).

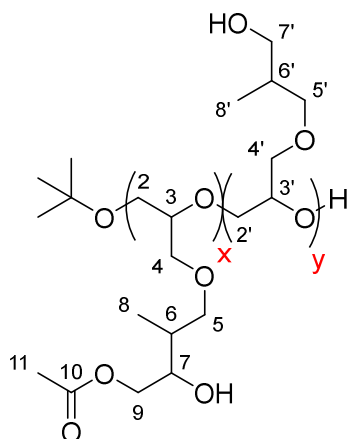
IR (ν , cm^{-1}): 3350, 2910, 2890, 1660, 1081, 866.

1H NMR (400 MHz, $CDCl_3$) δ ppm: **Initiator**, 1.19 (s, 9H, CH_3). **Section a**, 3.72–3.42 (m, 5H, H^{2-4}), 2.15 (br s, 1H, OH). **Section b**, 4.95 (s, 1H, H^{7a}), 4.89 (s, 1H, H^{7b}), 3.89 (s, 2H, H^5), 3.82–3.35 (m, 5H, $H^{2'-4'}$), 1.72 (s, 3H, H^8).

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: **Initiator**, not observed. **Section a**, 79.8* (C^3), 78.8* (C^3), 70.2, 69.9 (C^2 & C^4), **Section b**, 141.9 (H^6), 112.3 ($H^{7'}$), 79.8* ($C^{3'}$), 78.8* ($C^{3'}$), 75.3 (C^5), 70.2, 69.9 (C^2 & C^4), 19.4 (H^8).

GPC: M_n = 8260, M_w = 10420, D = 1.26

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-hydroxy-3-methyl-4-(oxiran-2-ylmethoxy)butyl acetate]-co-[2-({propan-3-ol}methyl)oxirane]



PMAGE-*graft*-AA-*graft*-OH

Formula: $C_4H_9O(C_{10}H_{18}O_5)_x(C_7H_{14}O_3)_y$

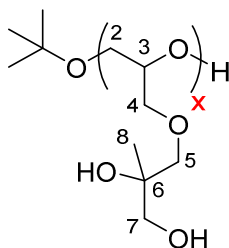
To a solution of PMAGE-**graft**-AA (30 mg, 0.20 mmol, 1.0 equiv) in 2.0 mL of THF was added $BH_3 \cdot DMS$ (20 μ L, 0.22 mmol, 1.1 equiv) dropwise at 0 °C and the mixture was stirred for 2 h. To the reaction mixture was added 3 N aqueous NaOH (0.30 mL, 0.90 mmol, 4.5 equiv) and aqueous 30% w/w H_2O_2 (0.1 mL, 0.60 mmol, 3.0 equiv), and the reaction mixture was left to stir at RT for 2 h. THF was removed under vacuum and crude mixture purified using size exclusion chromatography, LH-20 (MeOH) furnishing PMAGE-*graft*-AA-*graft*-OH as a clear oil (34 mg, 85%).

IR (ν , cm^{-1}): 3260, 2906, 2877, 2865, 1736, 1091.

1H NMR (400 MHz, Methanol- d_4) δ ppm: **Initiator**, 1.16 (s, 9H, CH_3). **Section x**, 4.20-4.14 (m, 1H, H^7), 3.98-3.91 (m, 2H, H^9), 3.88–3.14 (m, 7H, H^{2-5}), 2.01–1.85 (m, 1H, H^6), 1.22 (s, 3H, H^{11}), 1.00-0.94 (m, 3H, H^8). **Section y**, 3.88–3.14 (m, 9H, $H^{2'-5'}$ and $H^{7'}$), 2.01–1.85 (m, 1H, H^6), 1.00-0.94 (m, 3H, H^8). **Overall Ratio (x:y)** = 30:70 (Average Mw per unit = 167.60 g.mol $^{-1}$).

^{13}C NMR (101 MHz, Methanol- d_4) δ ppm: **Initiator**, not observed. **Section x**, 175.3 (H^{10}), 78.9* (C^3), 78.8* (C^3), 73.8, 70.9, 71.0, 69.9, 64.3 (C^2 & C^4 & C^5 & C^9), 57.8 (C^7), 36.1 (C^6), 20.1 (C^{11}), 12.9 (C^8). **Section y**, 78.9* ($C^{3'}$), 78.8* ($C^{3'}$), 73.8, 70.9, 71.0, 69.9, 64.3 ($C^{2'}$ & $C^{4'}$ & $C^{5'}$ & $C^{9'}$), 36.1 ($C^{6'}$), 13.2 ($C^{8'}$).

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2-methyl-3-(oxiran-2-ylmethoxy)propane-1,2-diol]



PMAGE-*graft*-(OH)₂

Formula: C₄H₉O(C₇H₁₄O₄)_x

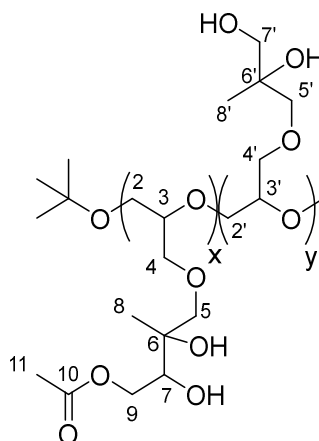
To a solution of PMAGE (56 mg, 0.44 mmol, 1.0 equiv) in 8.0 mL of water:*t*-BuOH (1:1 v/v) was added AD-mix- β (940 mg) at 0 °C and the mixture was stirred for 2 h. To the reaction mixture was added methanesulfonamide (42 mg, 0.44 mmol, 1.0 equiv) and the reaction mixture was left to stir at RT for 0.5 h. Solvent was removed under vacuum and crude mixture purified using size exclusion chromatography, LH-20 (MeOH) furnishing PMAGE-*graft*-(OH)₂ as a clear oil (50 mg, 70%).

IR (v, cm⁻¹): 3300, 2912, 2877, 2865, 1005.

¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: **Initiator**, not observable **Section x**, 3.87 – 3.25 (m, 10H, H²⁻⁴ and H⁵ and H⁷ and OH), 1.18 (s, 3H, H⁸).

¹³C NMR (101 MHz, Methanol-*d*₄) δ ppm: **Initiator**, not observed. **Section x**, 78.7* (C³), 78.6* (C³), 75.7 (C² or C⁴ or C⁵ or C⁷), 72.2 (C⁶), 71.3, 69.8, 69.5 (C² & C⁴ & C⁵ & C⁷), 20.7 (C⁸).

Polyether: α -*tert*-Butyl- ω -hydroxy-poly[2,3-dihydroxy-3-methyl-4-(oxiran-2-ylmethoxy)butyl acetate]-co-[2-methyl-3-(oxiran-2-ylmethoxy)propane-1,2-diol]



PMAGE-*graft*-AA-*graft*-(OH)₂

Formula: C₄H₉O(C₁₀H₁₈O₆)_x(C₇H₁₄O₄)_y

To a solution of PMAGE-*graft*-AA (50 mg, 0.33 mmol, 1.0 equiv) in 6.0 mL of water:*t*-BuOH (1:1 v/v) was added AD-mix- β (705 mg) at 0 °C and the mixture was stirred for 2 h. To the reaction mixture was added methanesulfonamide (32 mg, 0.44 mmol, 1.0 equiv) and the reaction mixture was left to stir at RT for 0.5 h. Solvent was removed under vacuum and crude mixture purified using size exclusion chromatography, LH-20 (MeOH) furnishing PMAGE-*graft*-AA-*graft*-(OH)₂ as a clear oil (42 mg, 70%).

IR (ν , cm⁻¹): 3300, 2904, 2877, 2899, 1782, 1013.

¹H NMR (400 MHz, Methanol-*d*₄) δ ppm: **Initiator**, not observable **Section x**, 3.74 – 3.17 (m, 12H, H²⁻⁴ & H⁵ & H⁷ & H⁹ & 2OH), 1.32 (s, 3H, H¹¹), 1.09 (s, 3H, H⁸). **Section y**, 3.74 – 3.17 (m, 10H, H^{2'-4'} and H^{5'-7'}), 1.05 (s, 3H, H⁸). **Overall Ratio (x;y)** = 30:70 (Average Mw per unit = 182.20 g.mol⁻¹).

¹³C NMR (101 MHz, Methanol-*d*₄) δ ppm: **Initiator**, not observed. **Section x**, 78.7* (C³), 78.6* (C³), 75.7 (C^{2'} or C^{4'} or C^{5'} or C^{9'}), 72.2 (C⁶), 71.3, 69.8, 69.6, 66.5 (C^{2'} & C^{4'} & C^{5'} & C^{9'}), 20.9 (C¹¹), 20.7 (C⁸). **Section y**, 78.7* (C³), 78.6* (C³), 75.7 (C^{2'} & C^{4'} & C^{5'} & C^{7'}), 72.2 (C⁶), 69.8, 69.6, 66.5 (C^{2'} & C^{4'} & C^{5'} & C^{7'}), 20.7 (C⁸).

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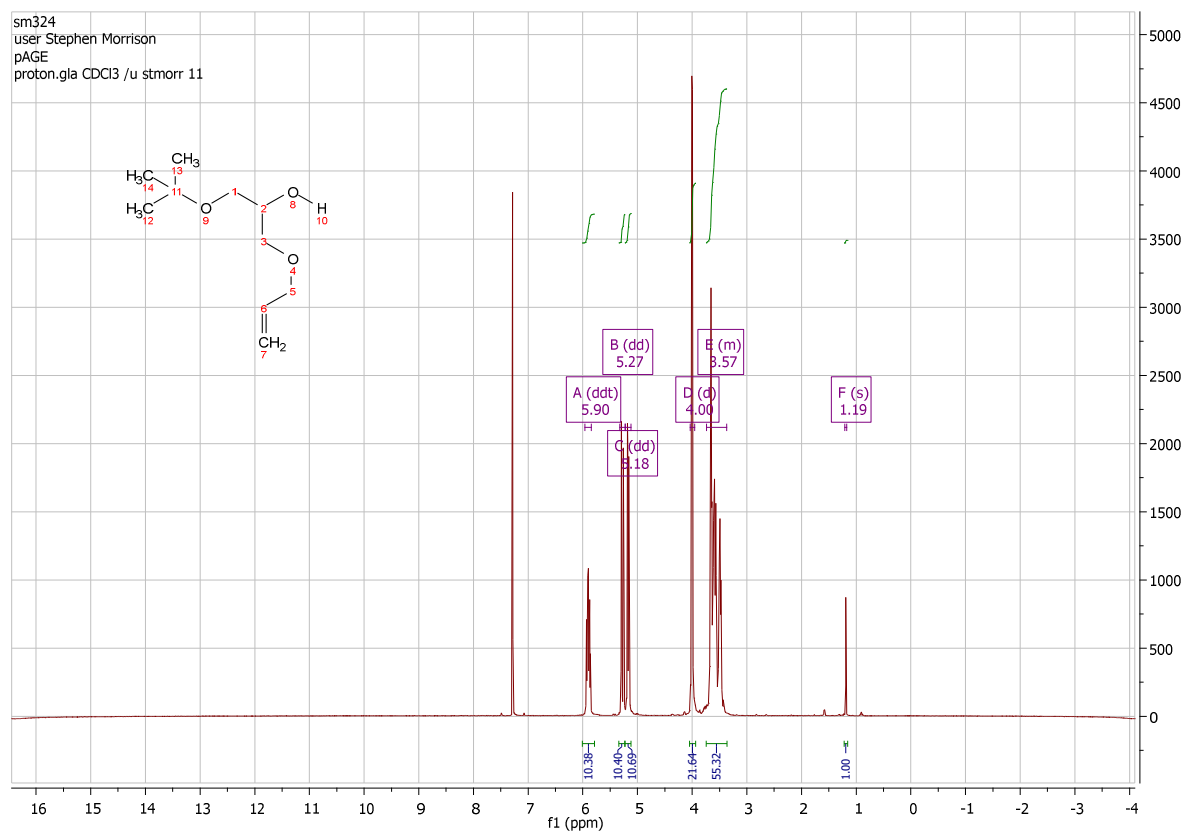
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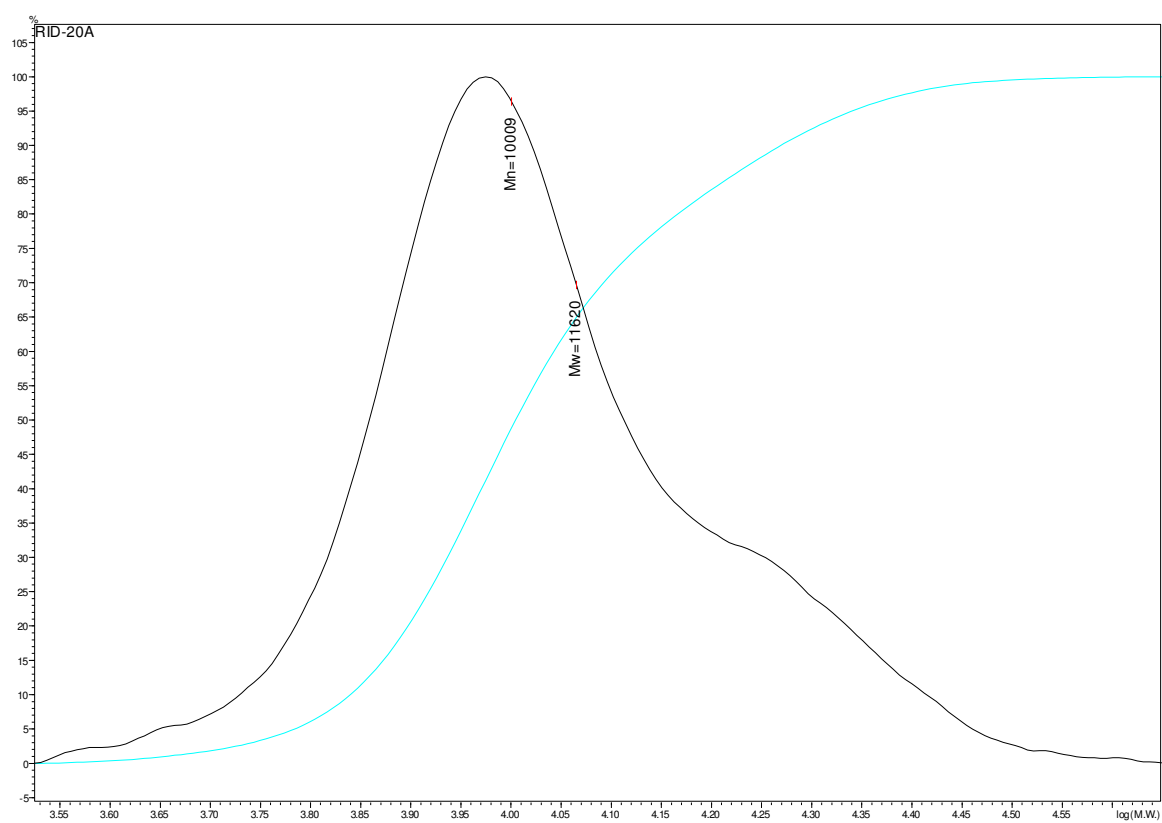
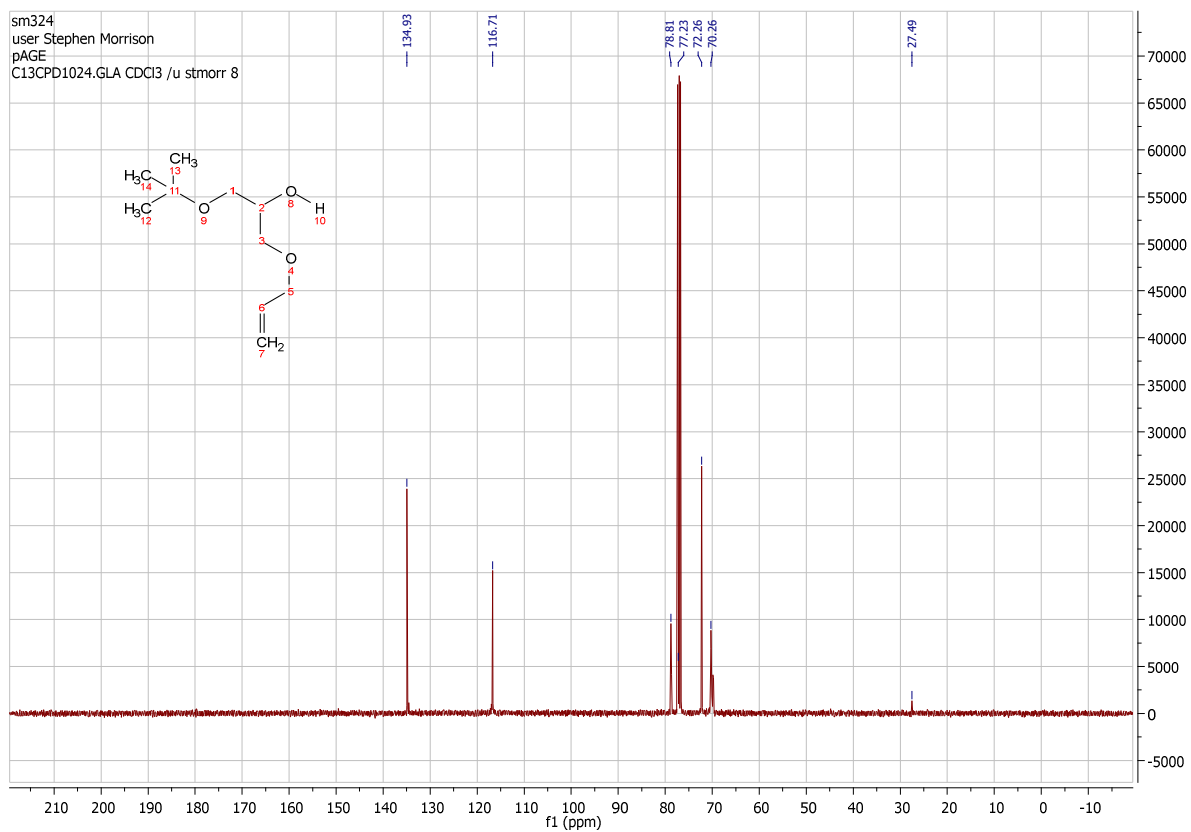
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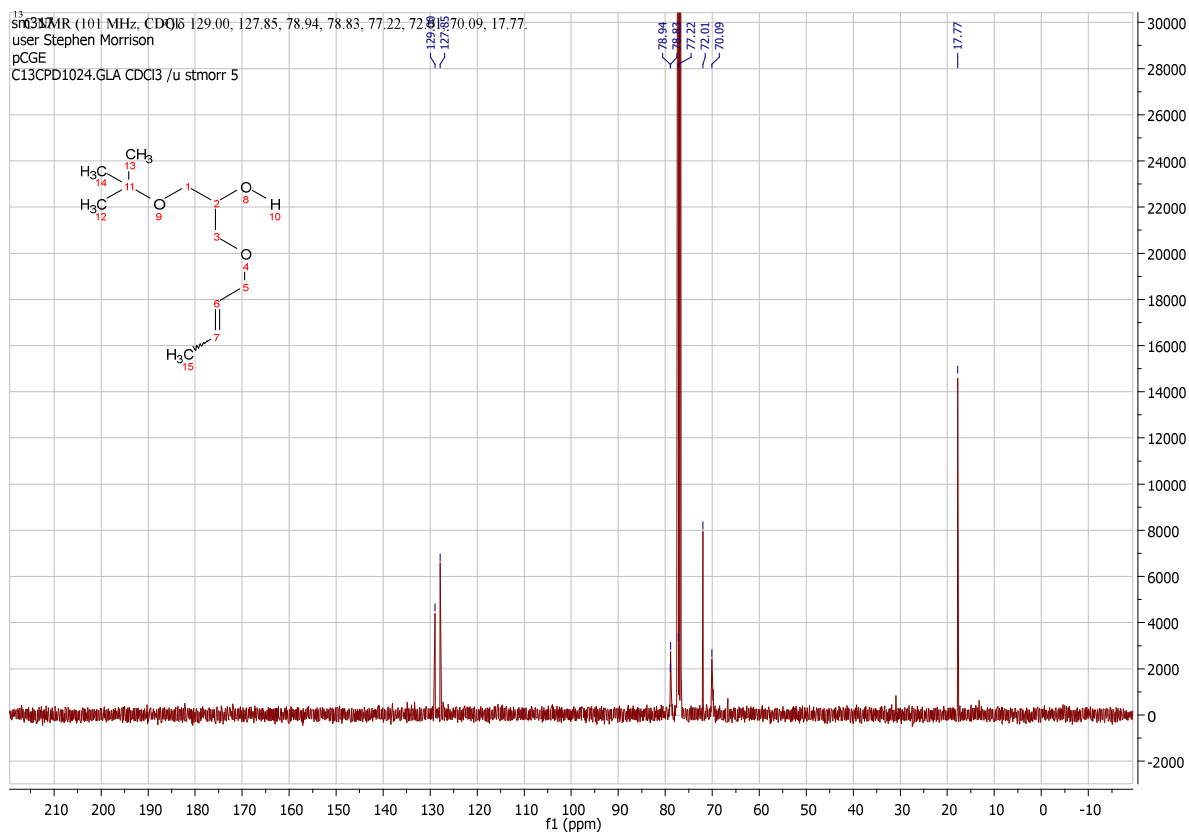
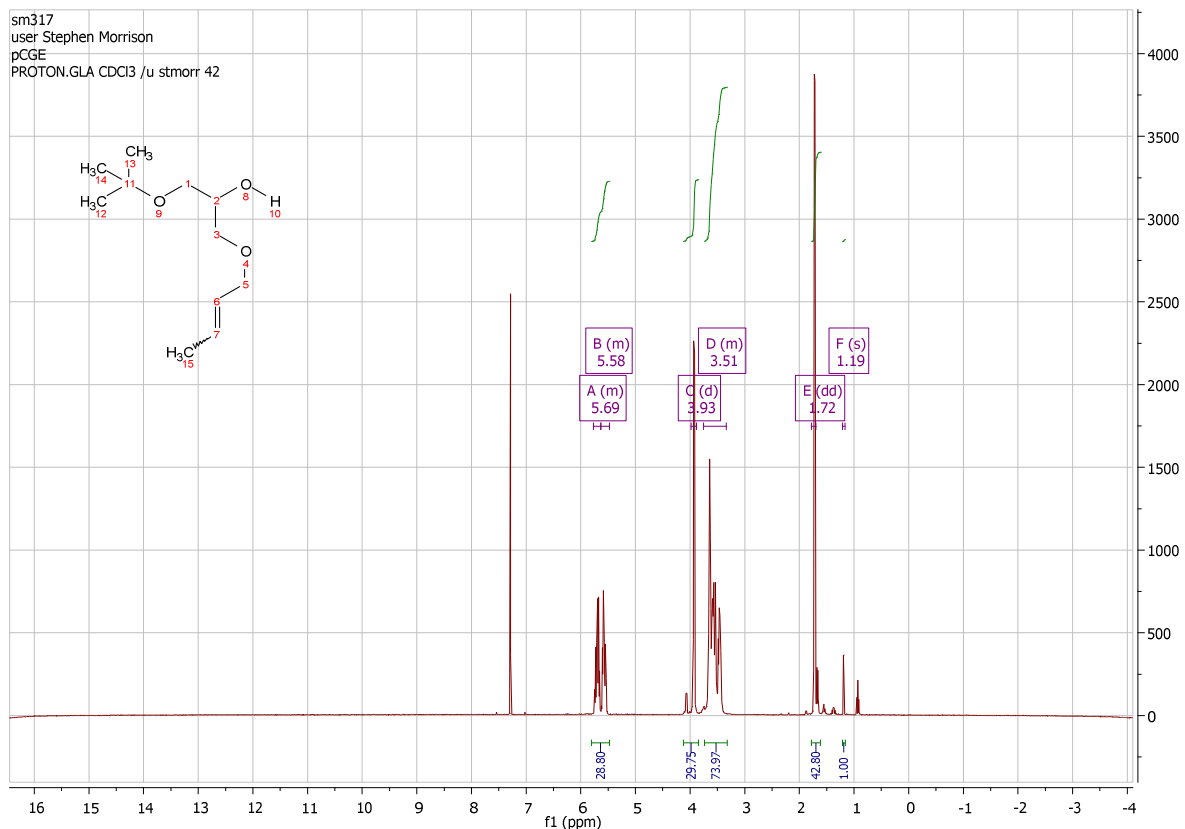
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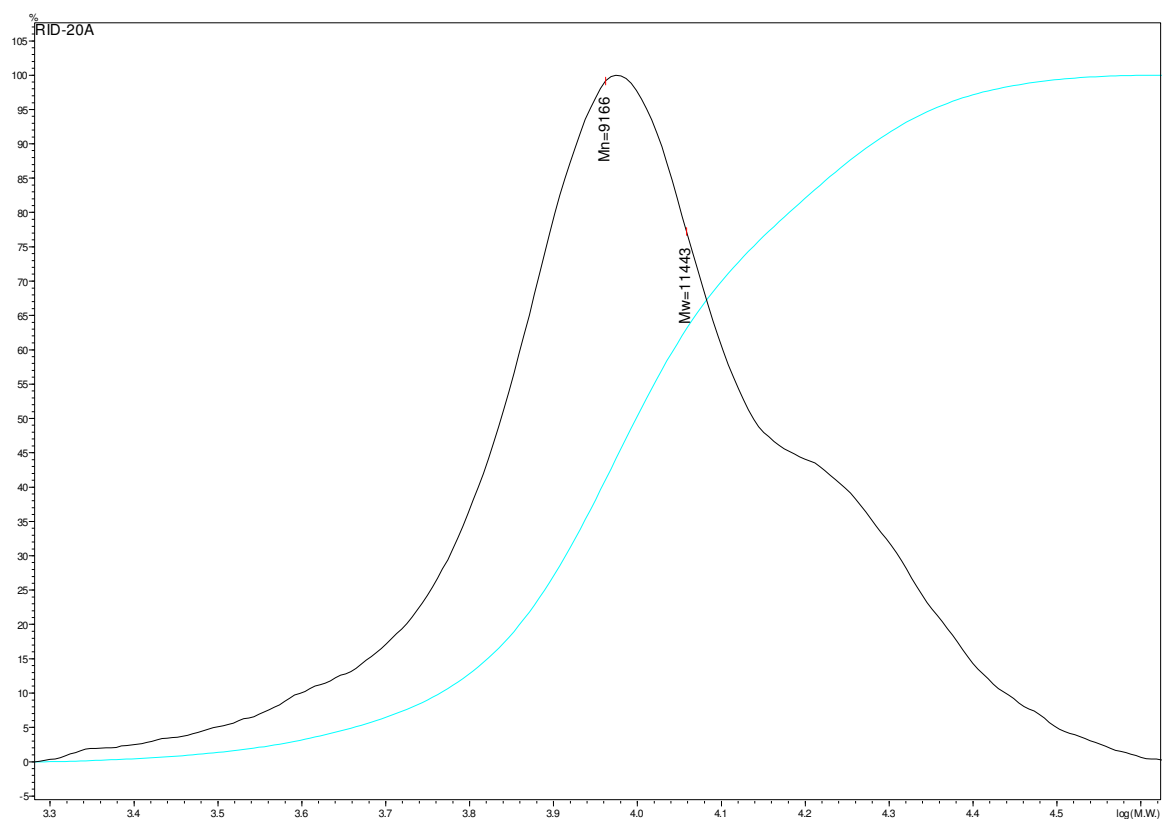
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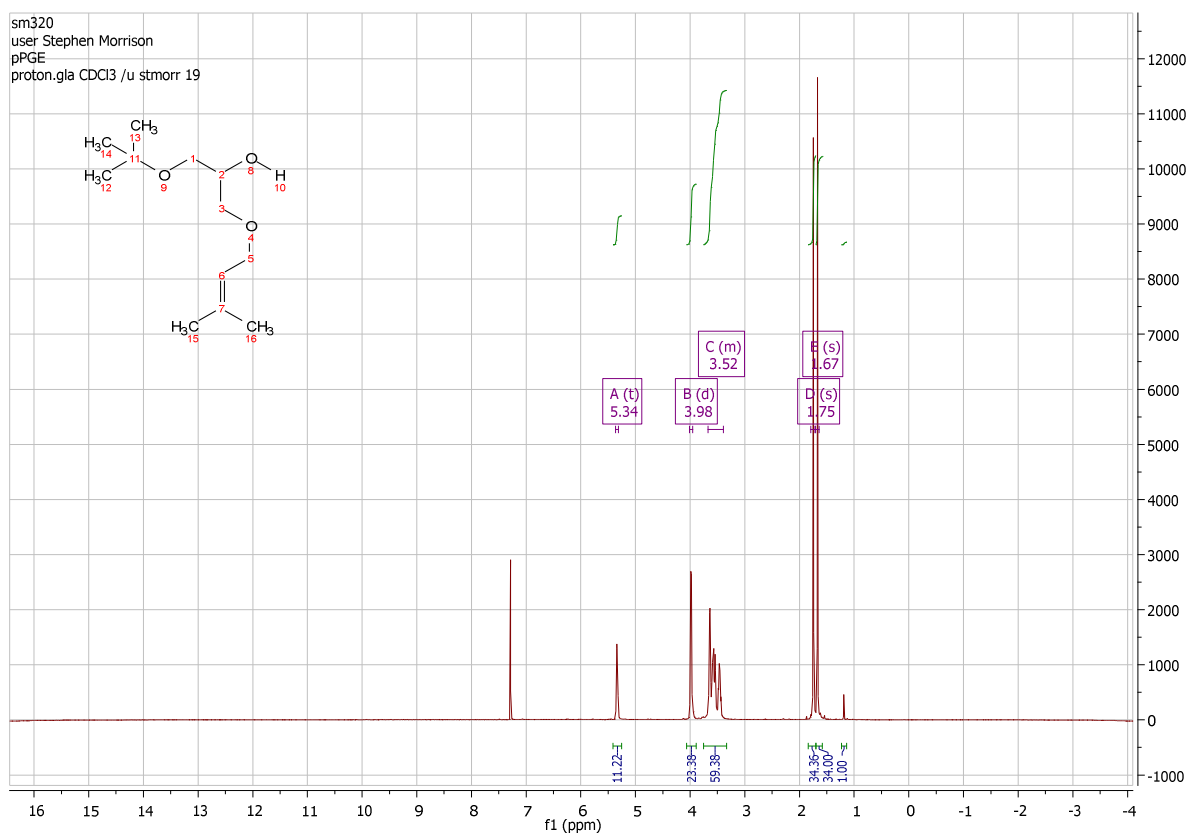


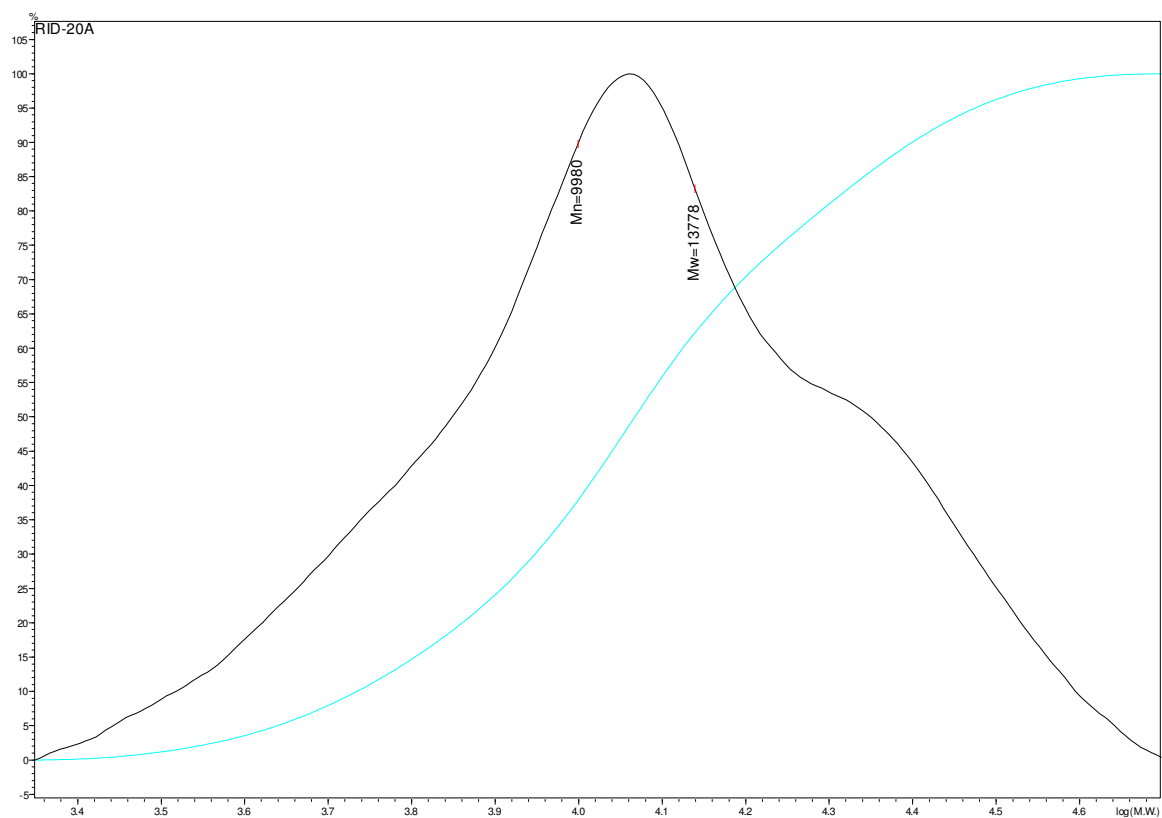
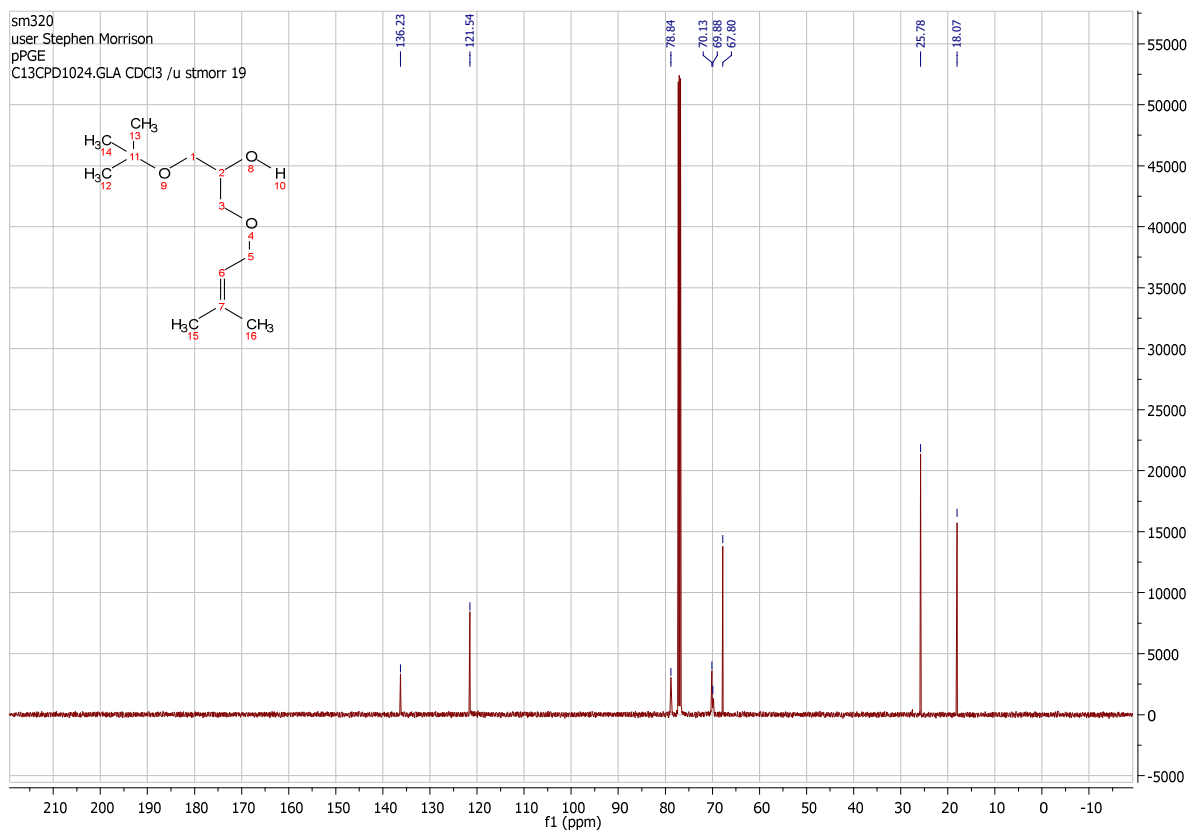
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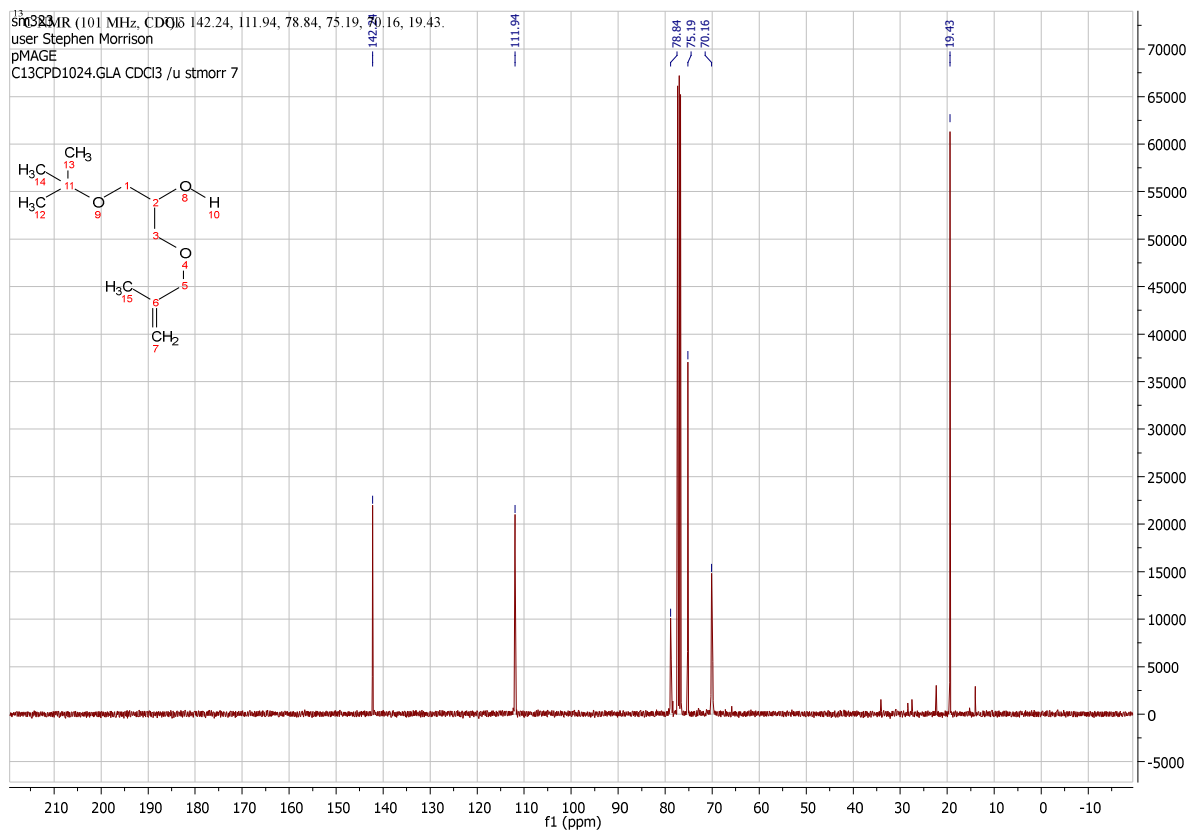
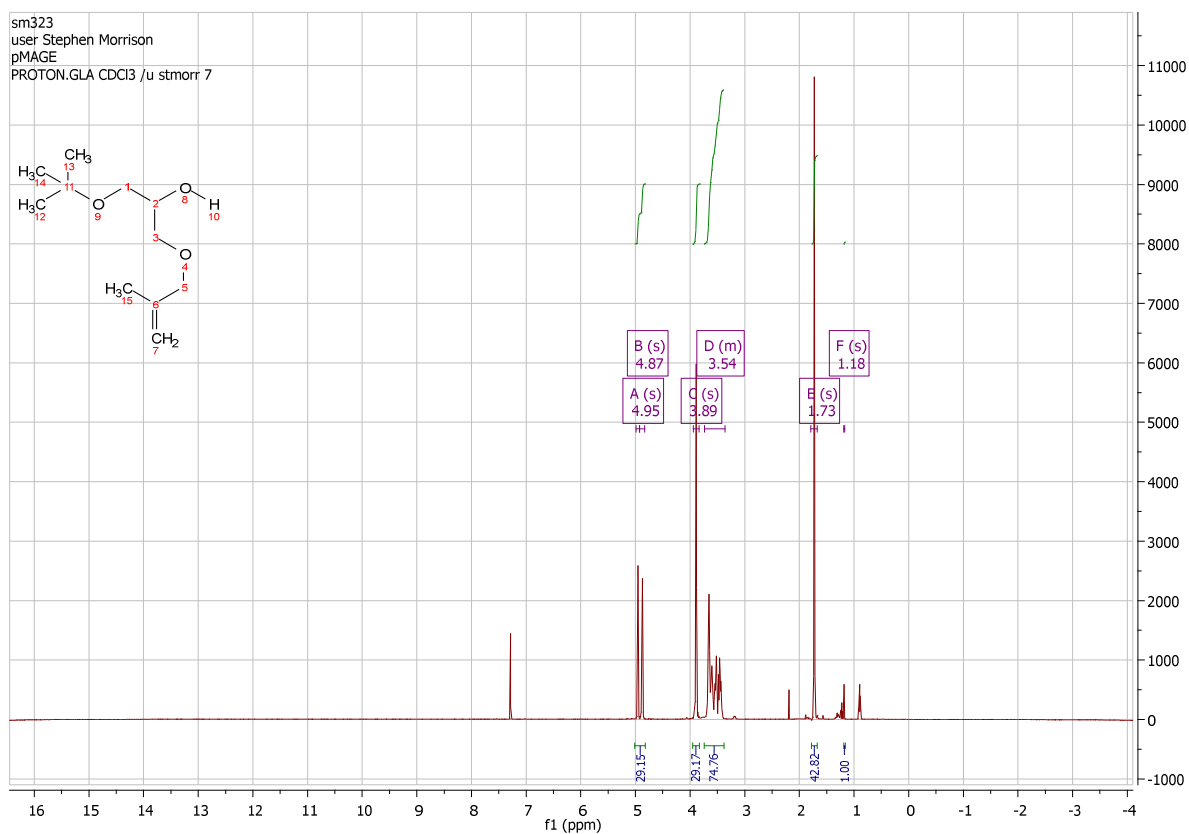


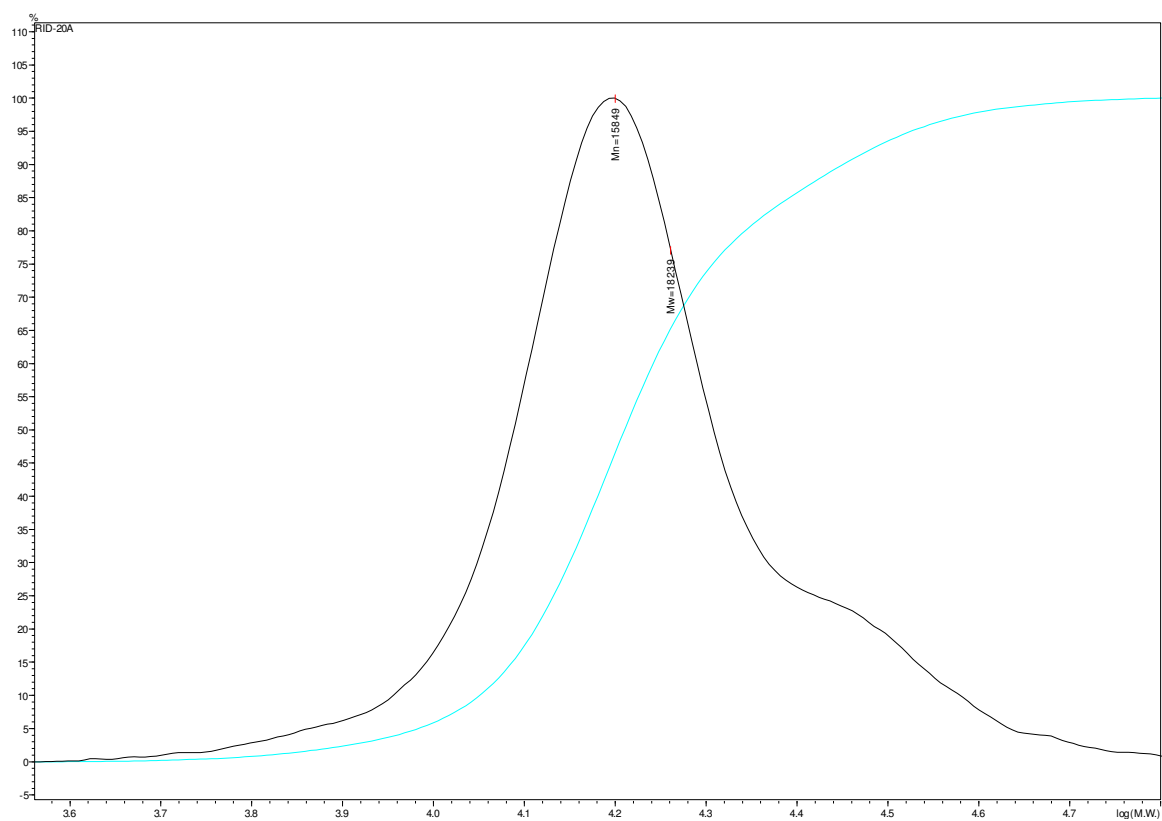
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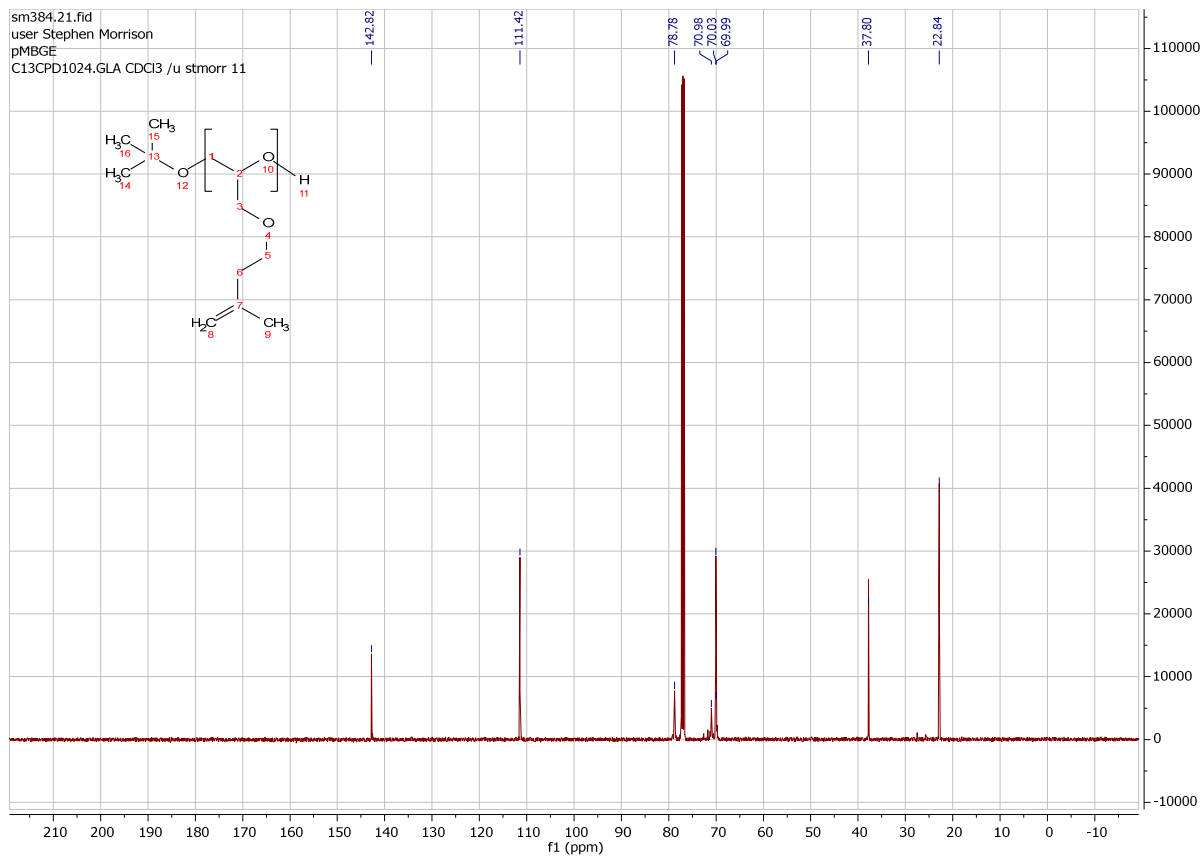
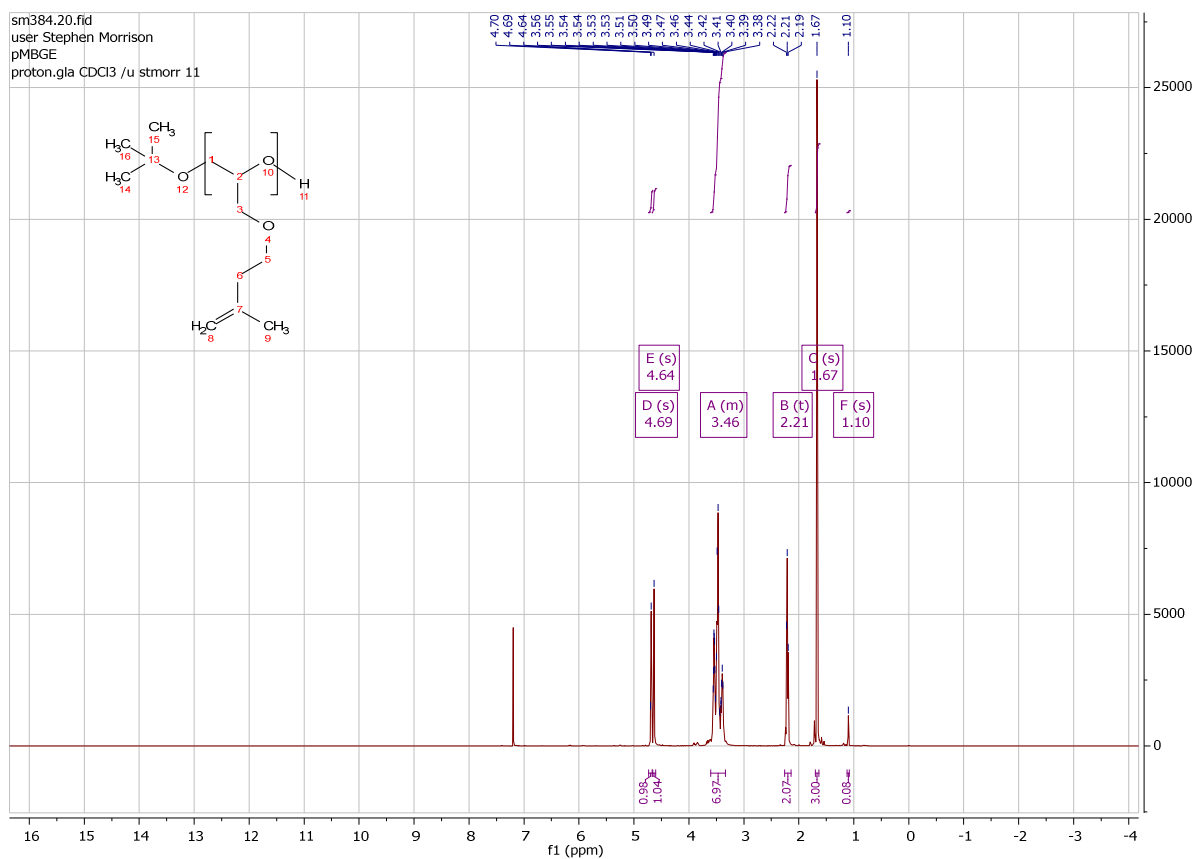


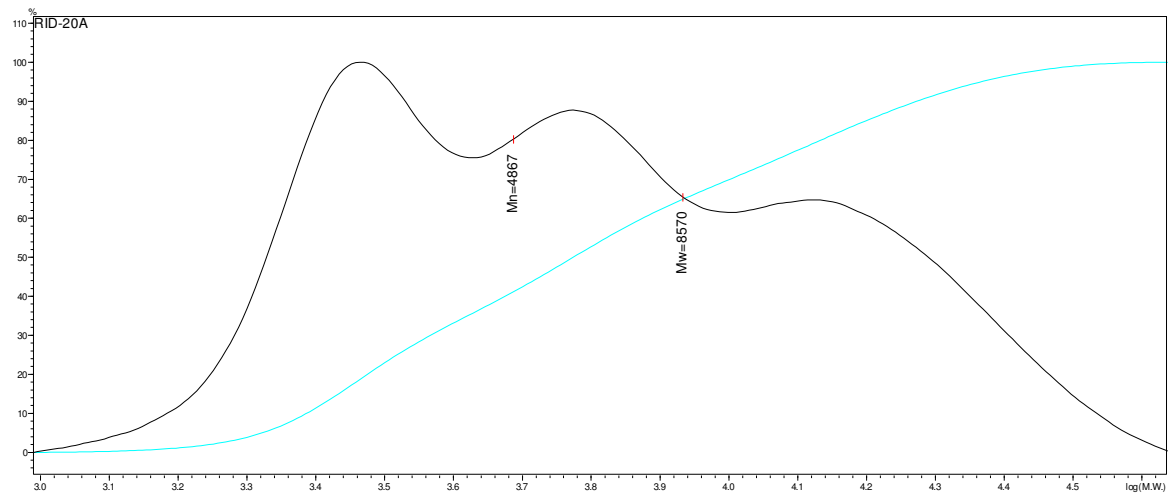
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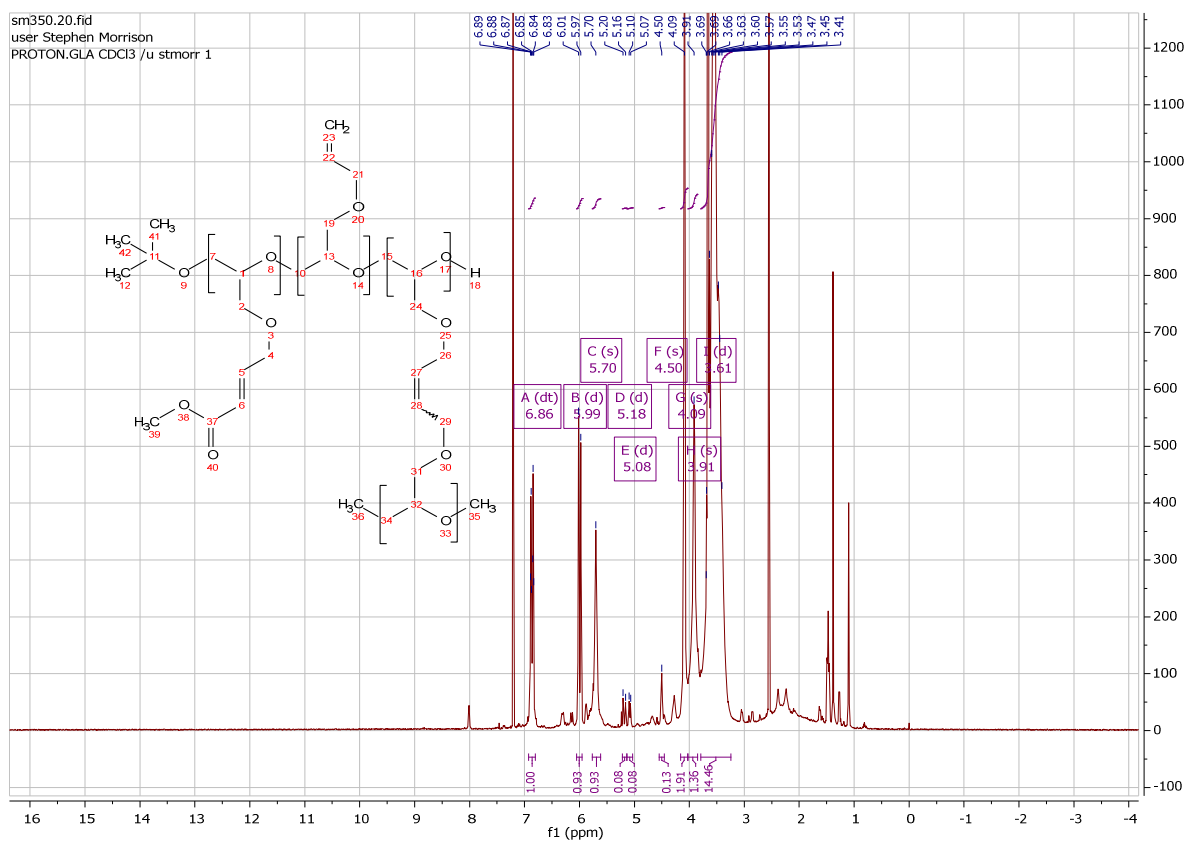
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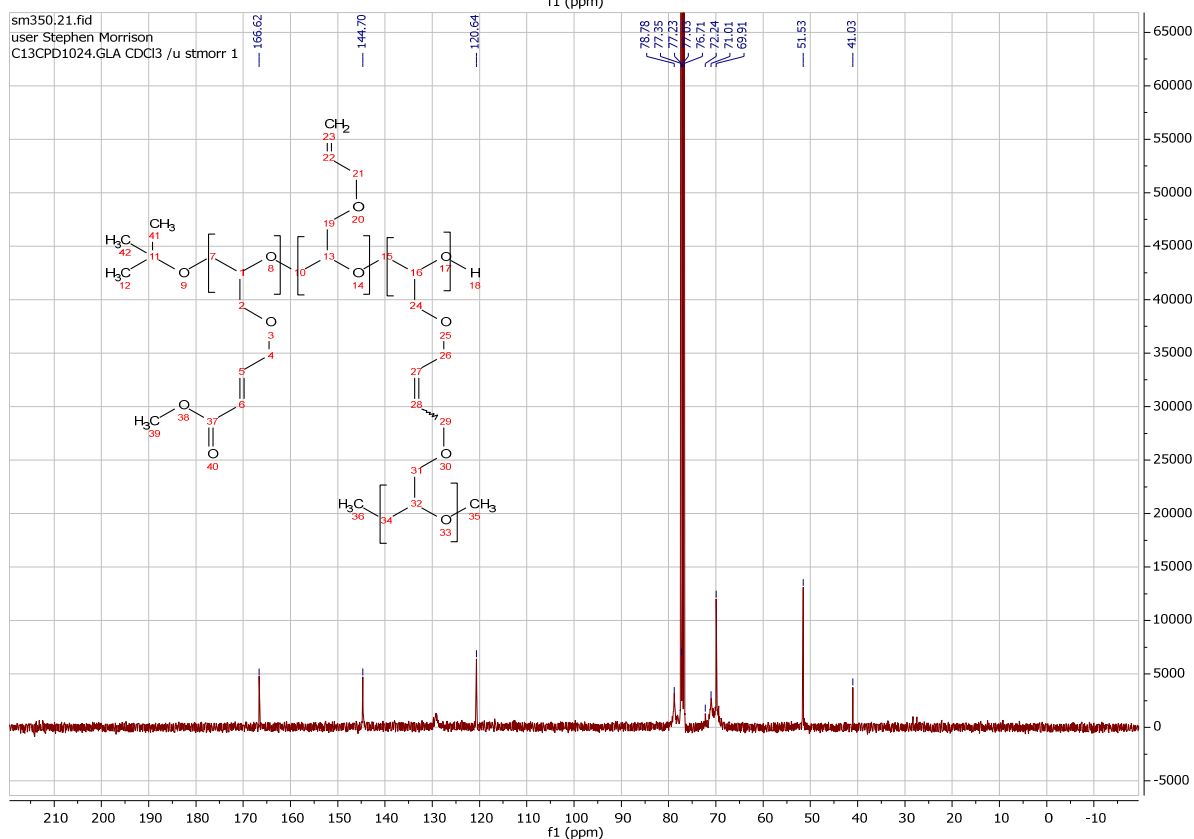


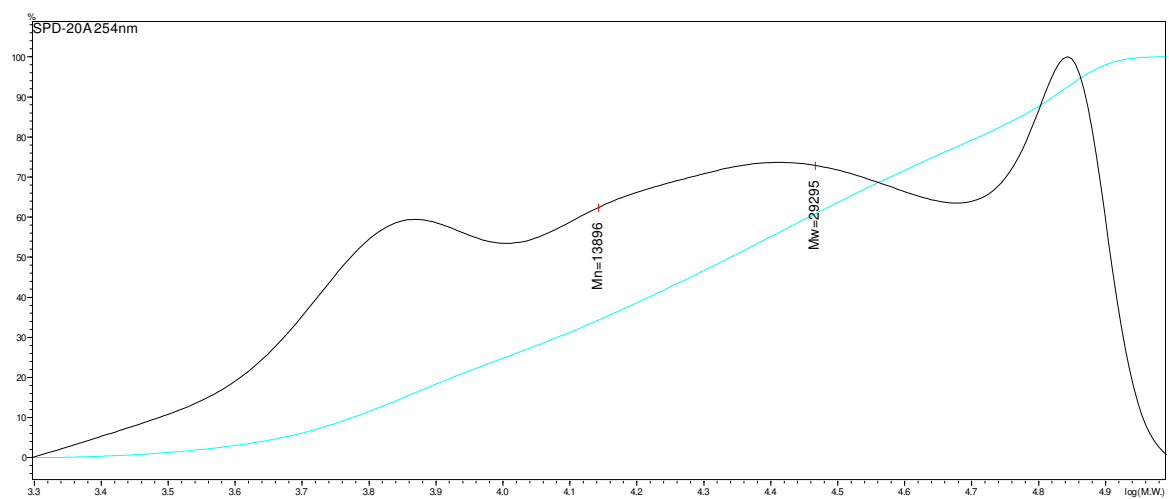
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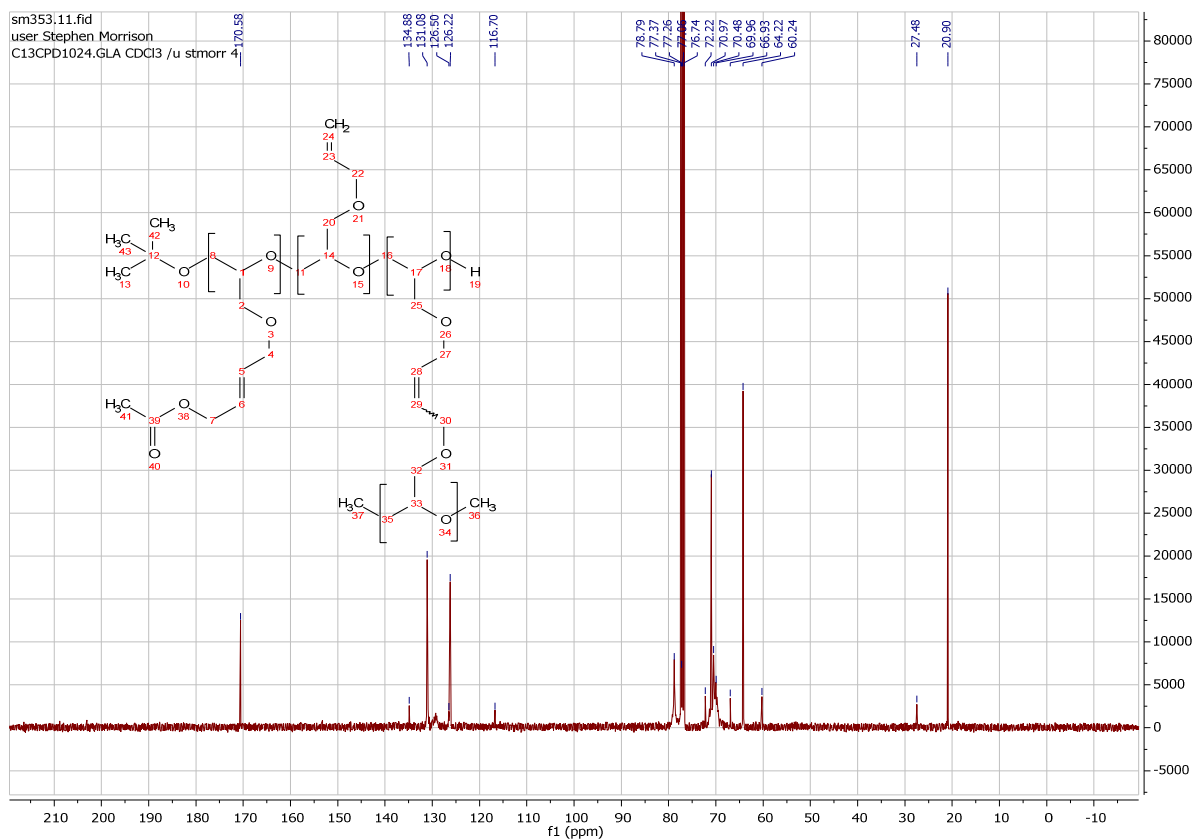


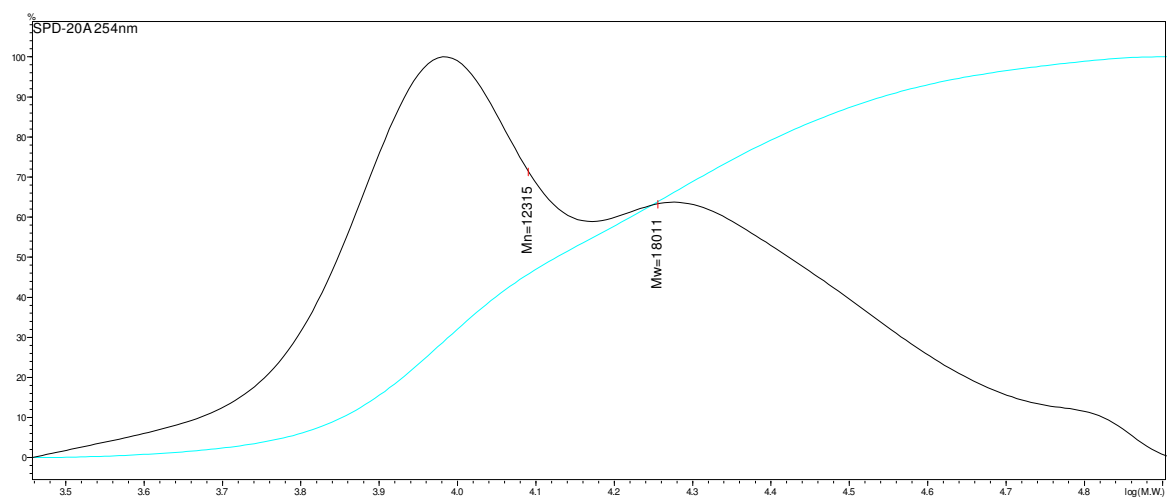
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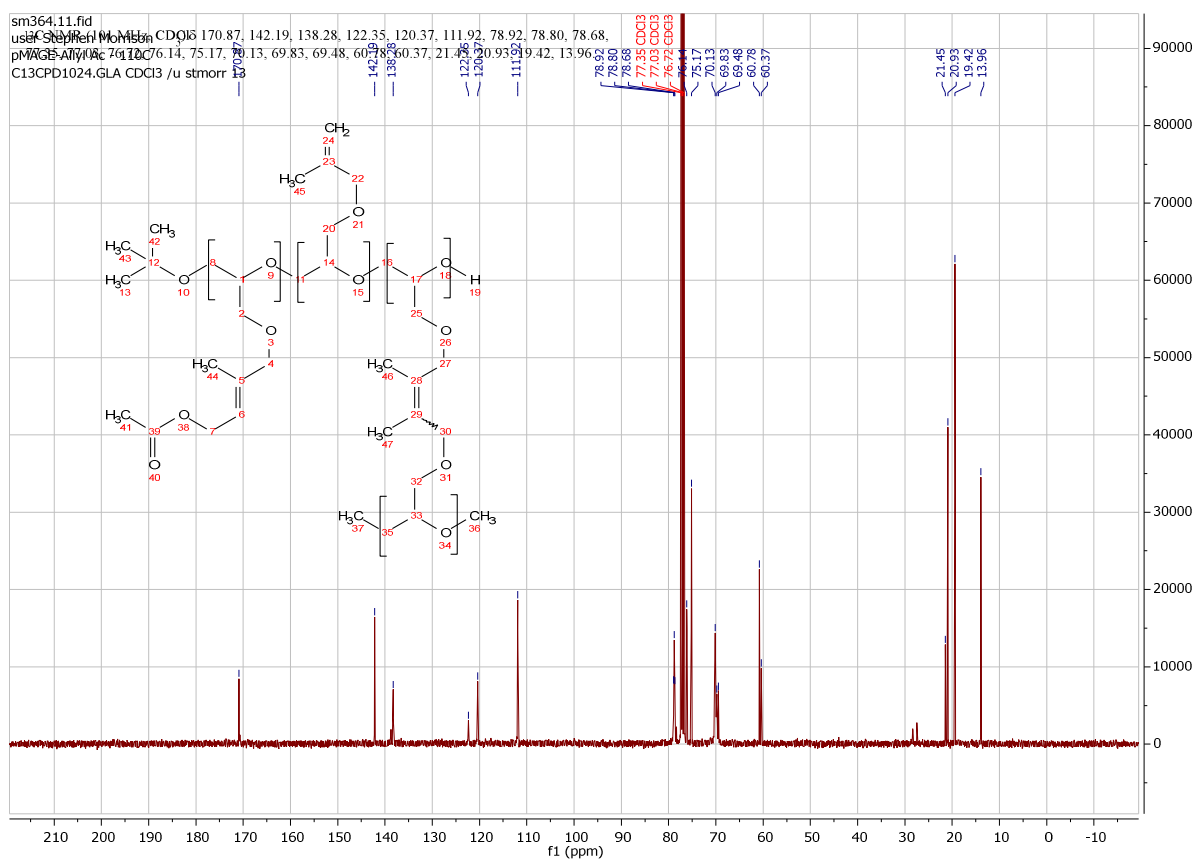
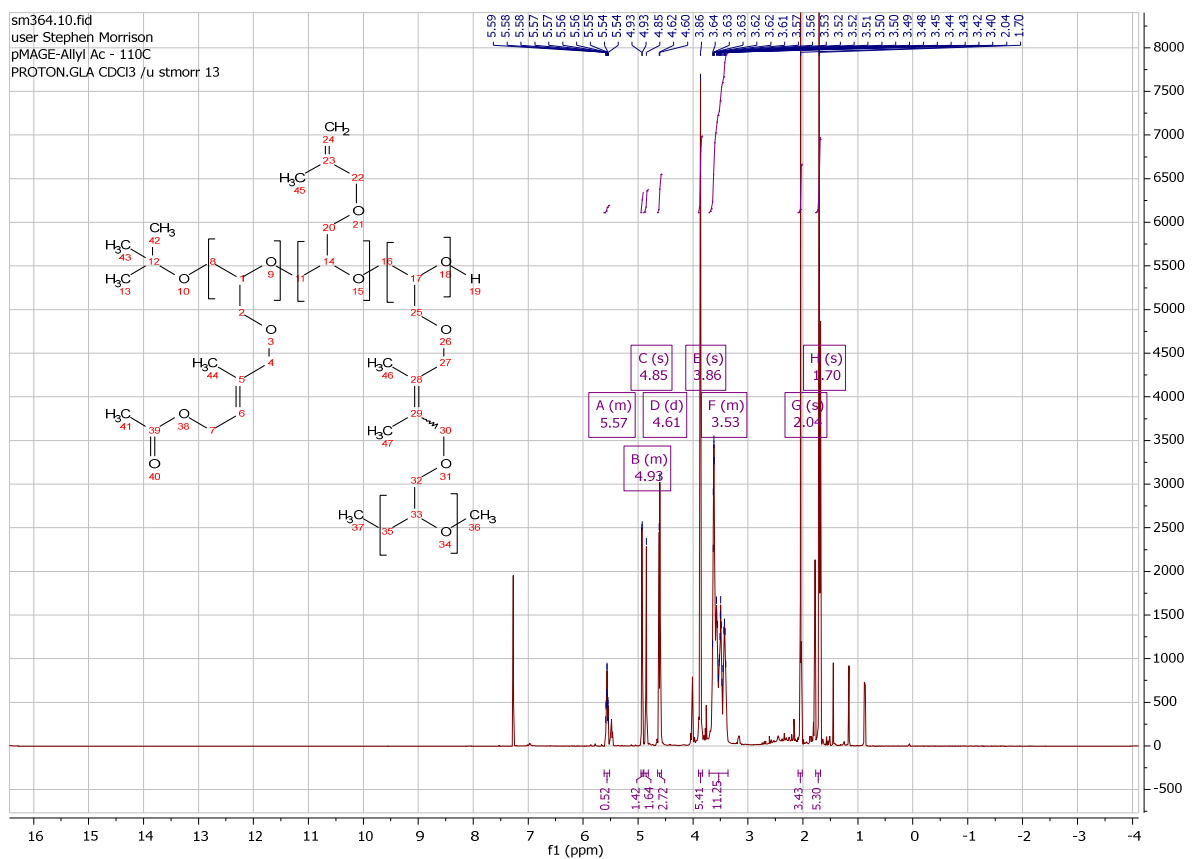


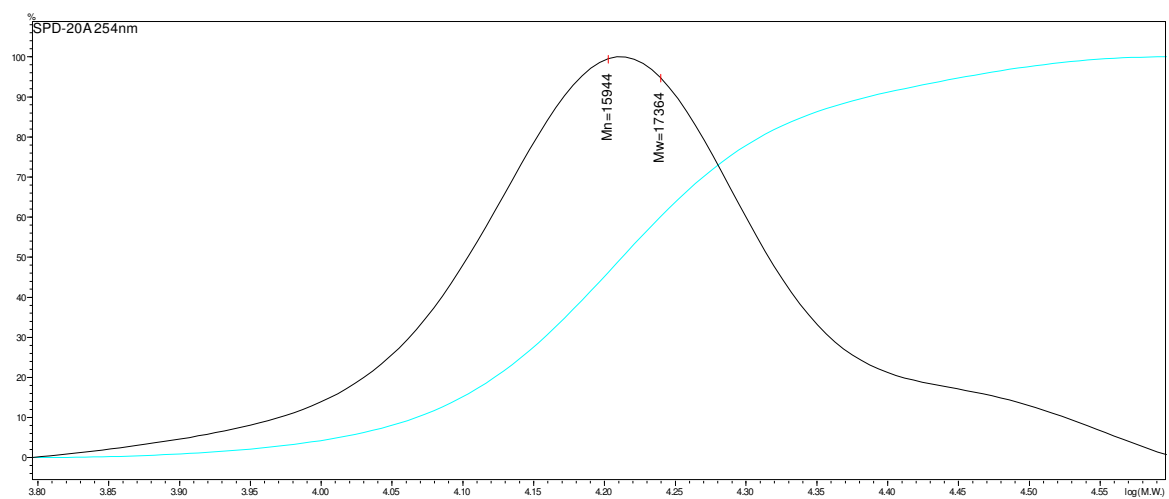
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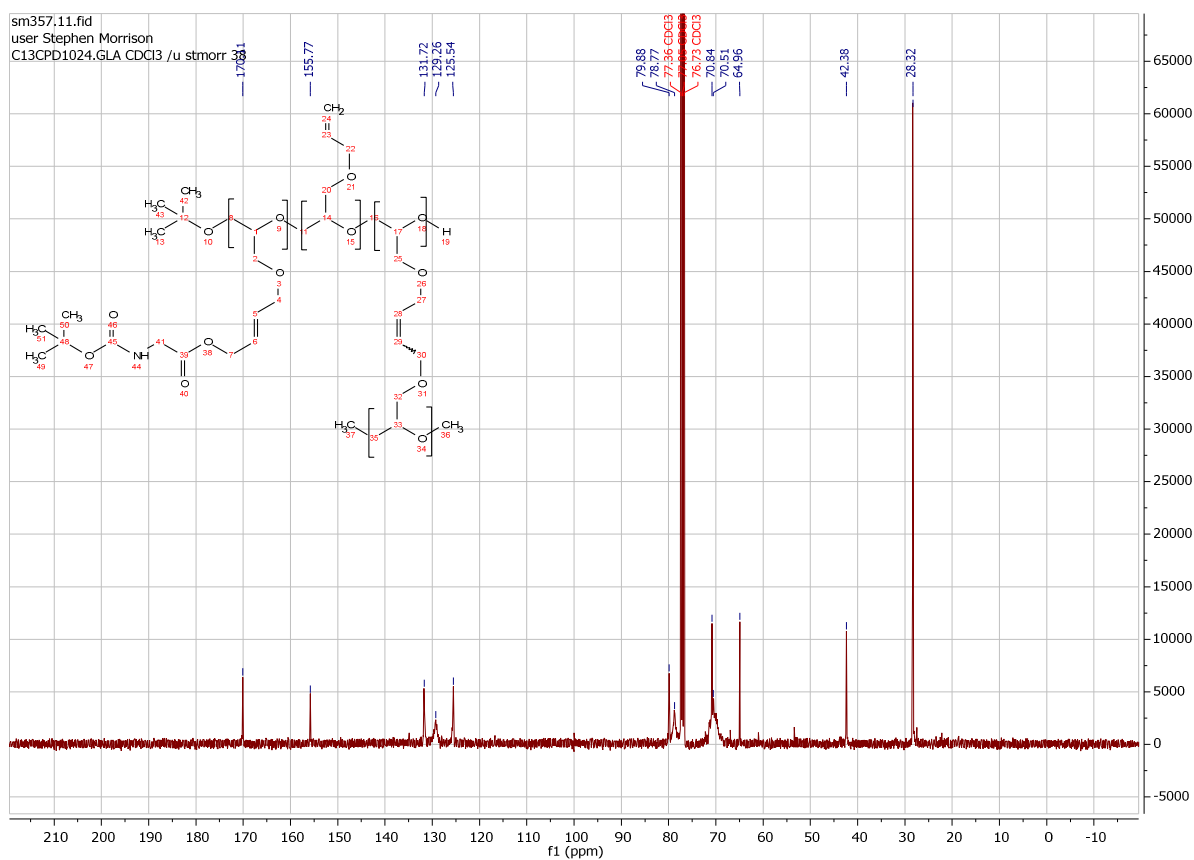
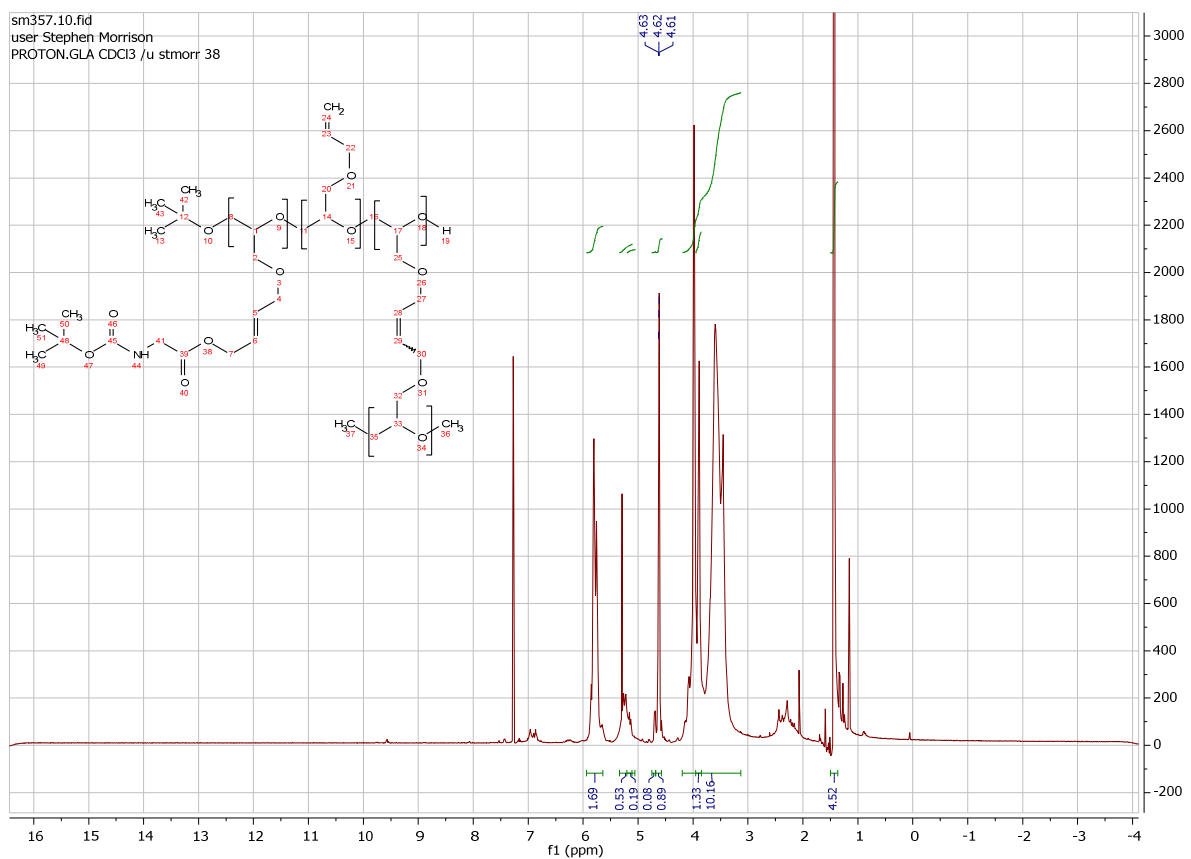


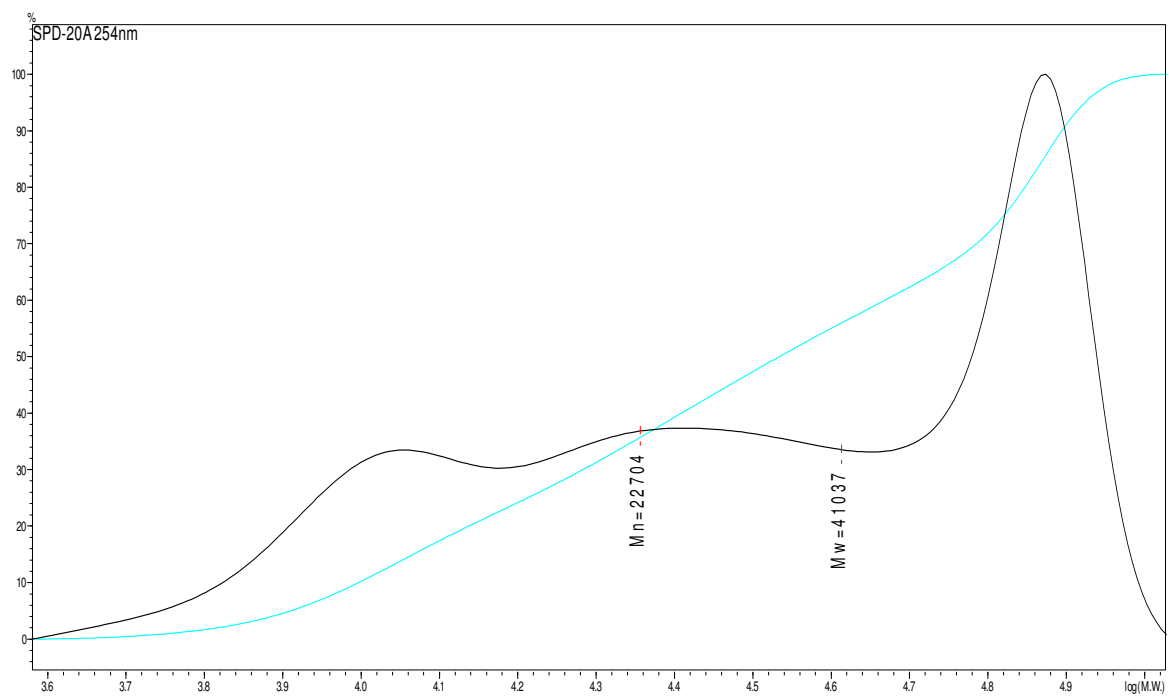
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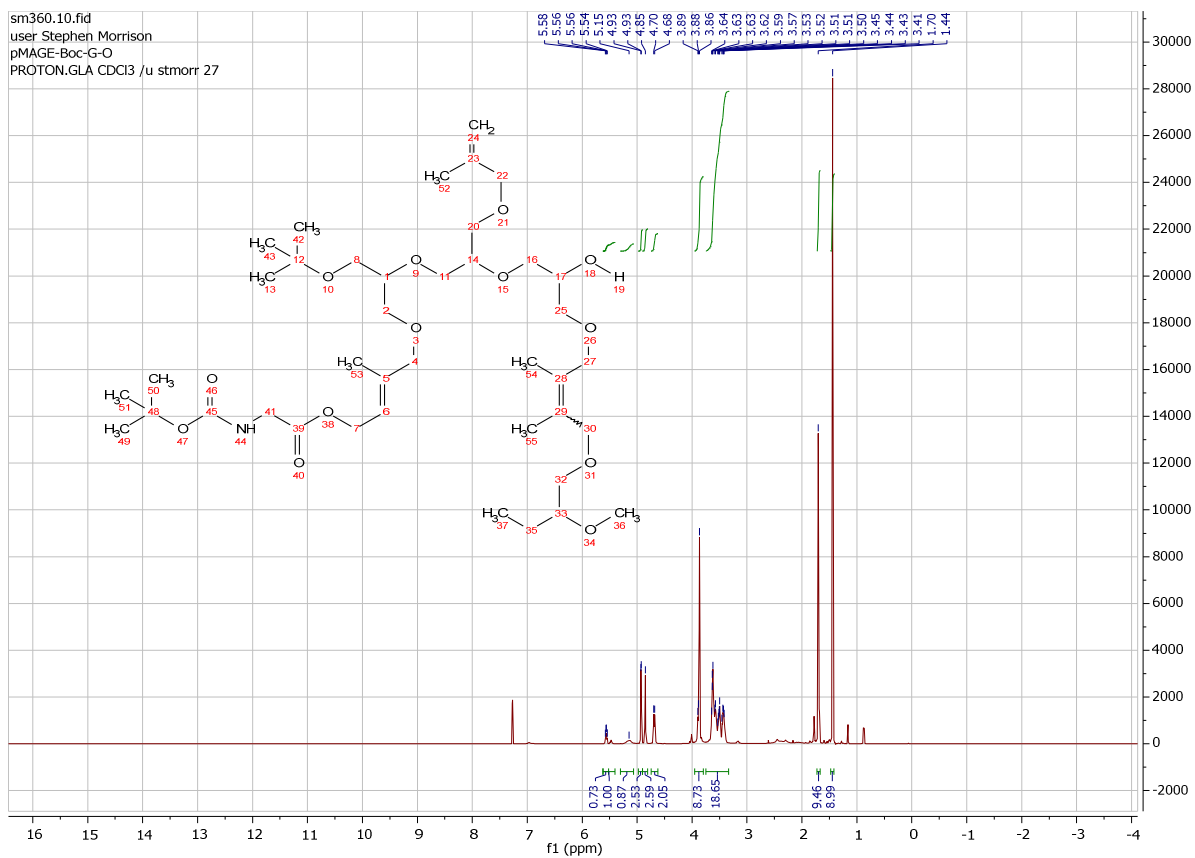


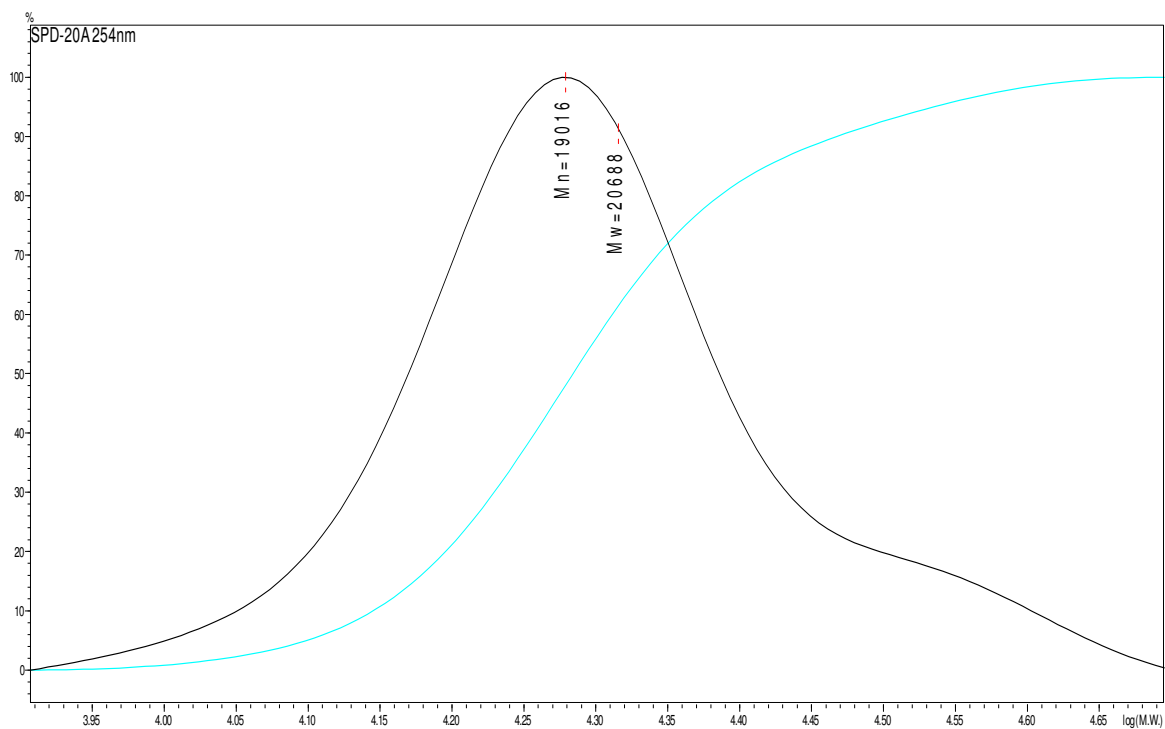
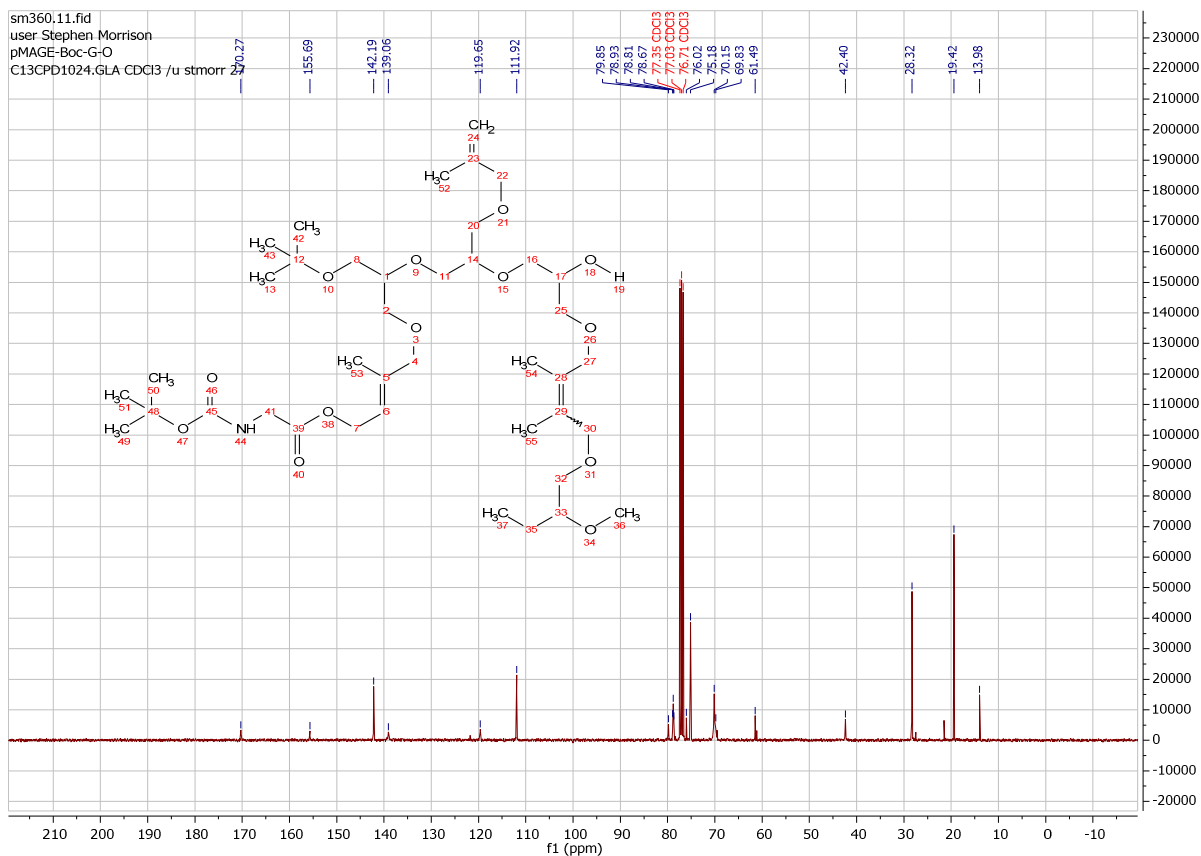
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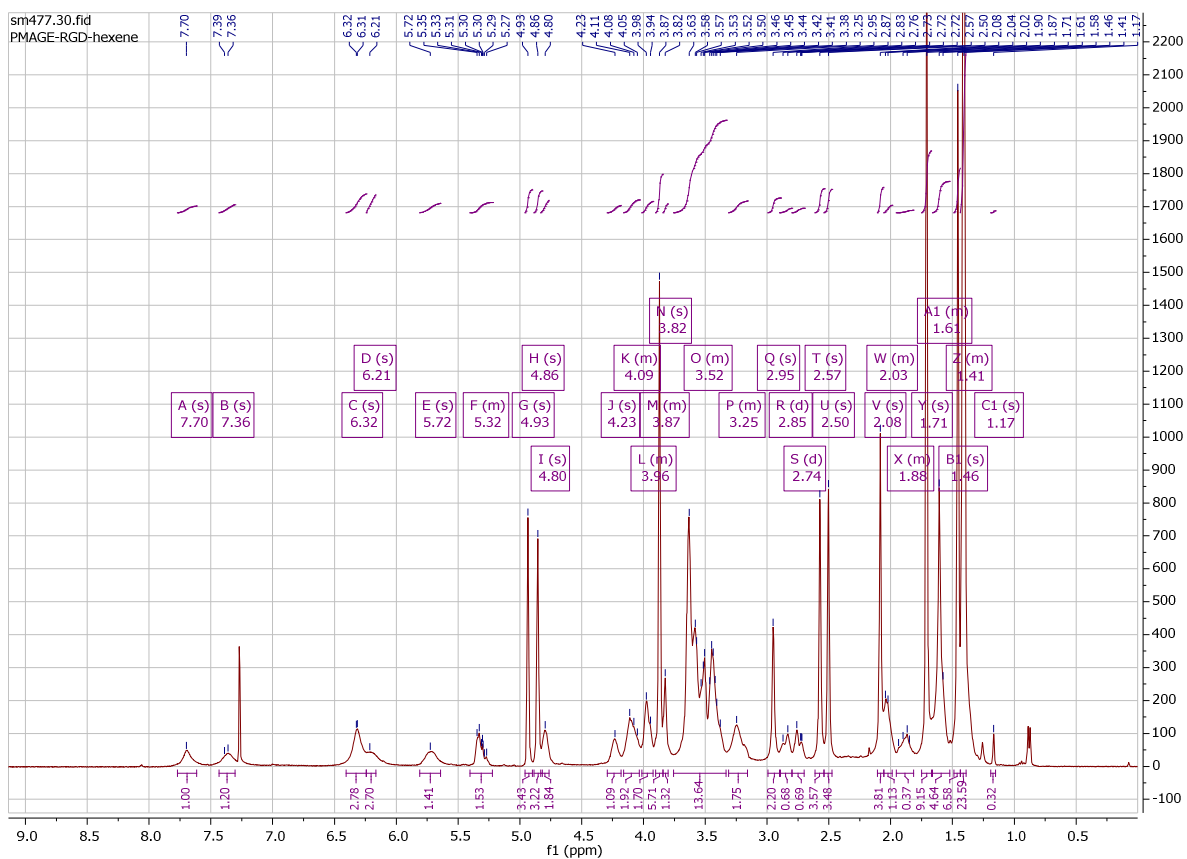


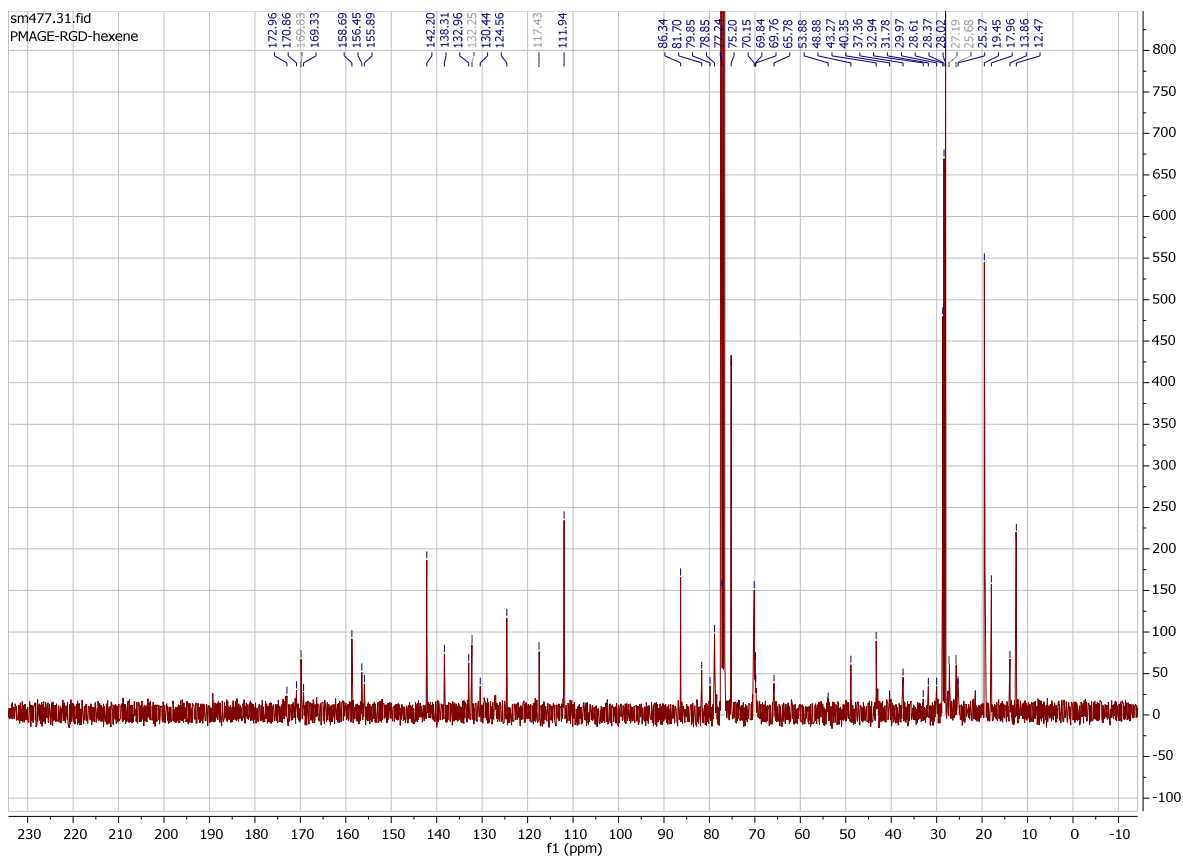
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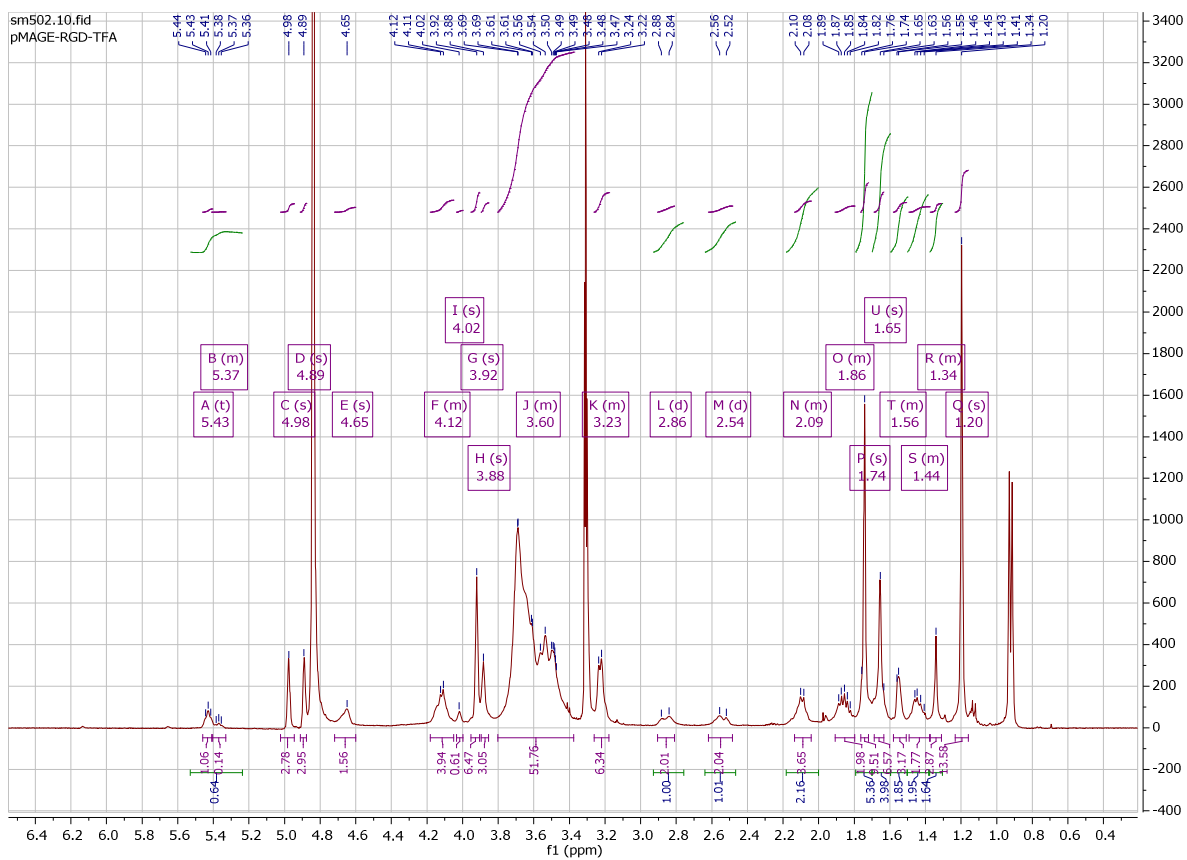


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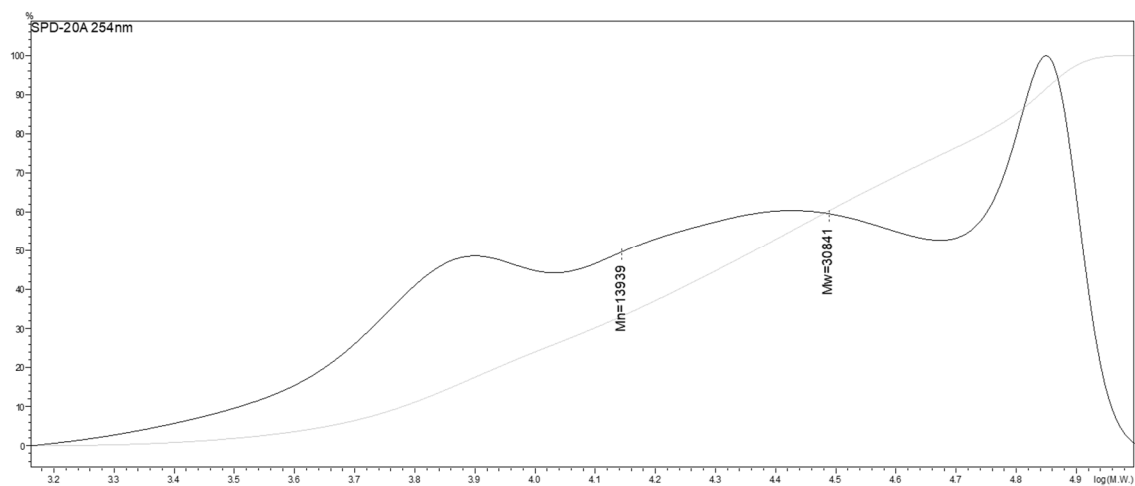




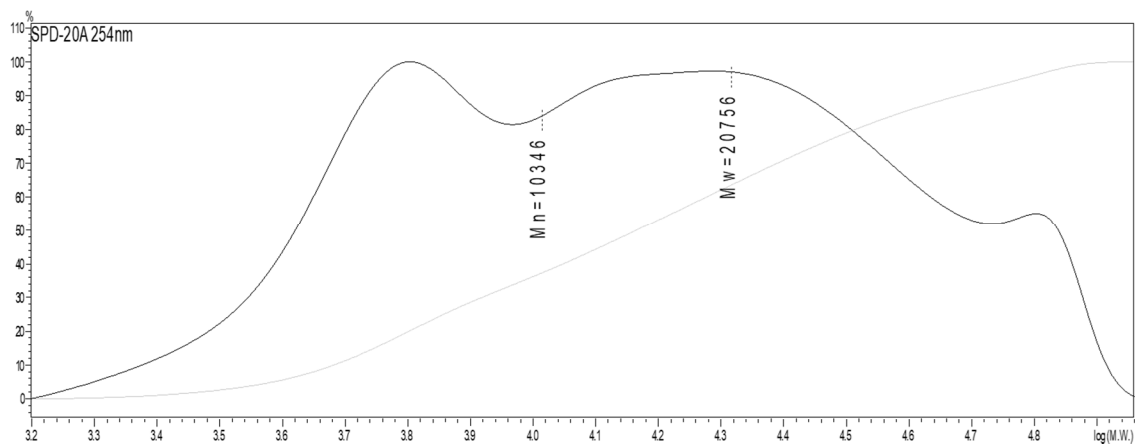
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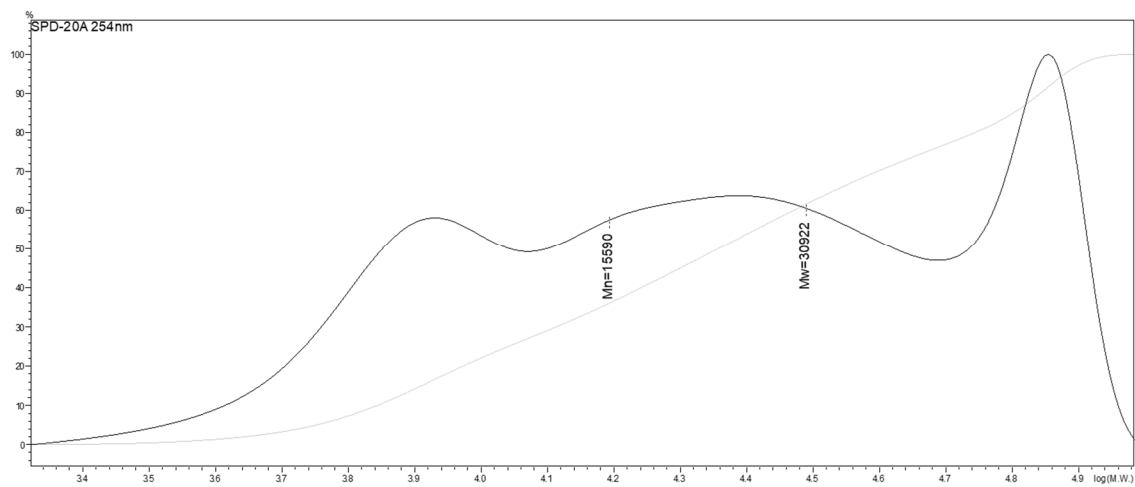
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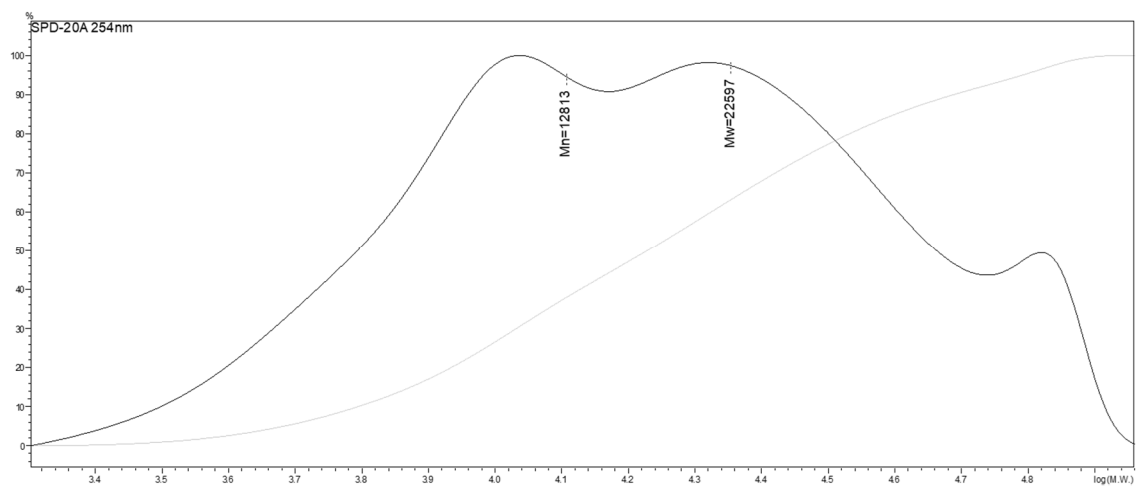
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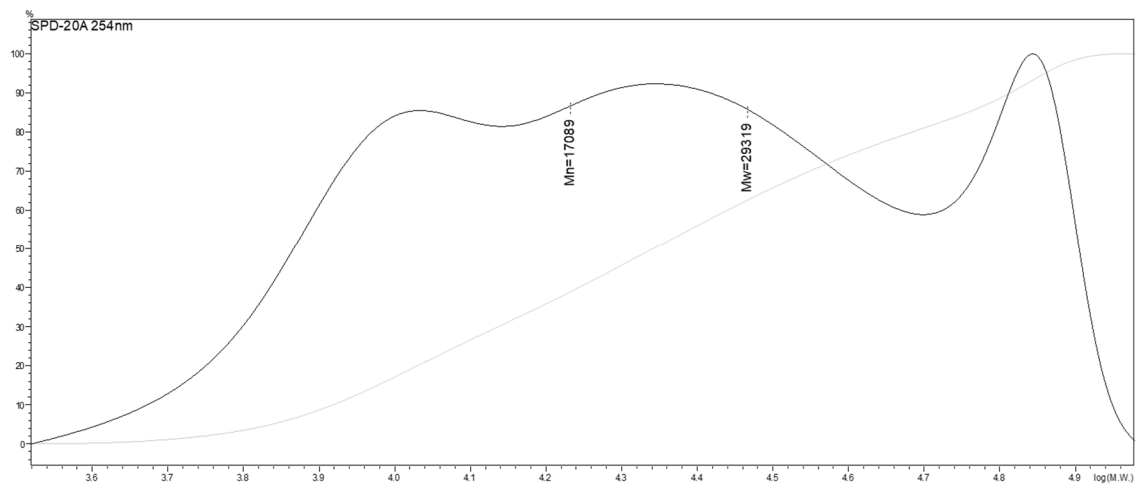
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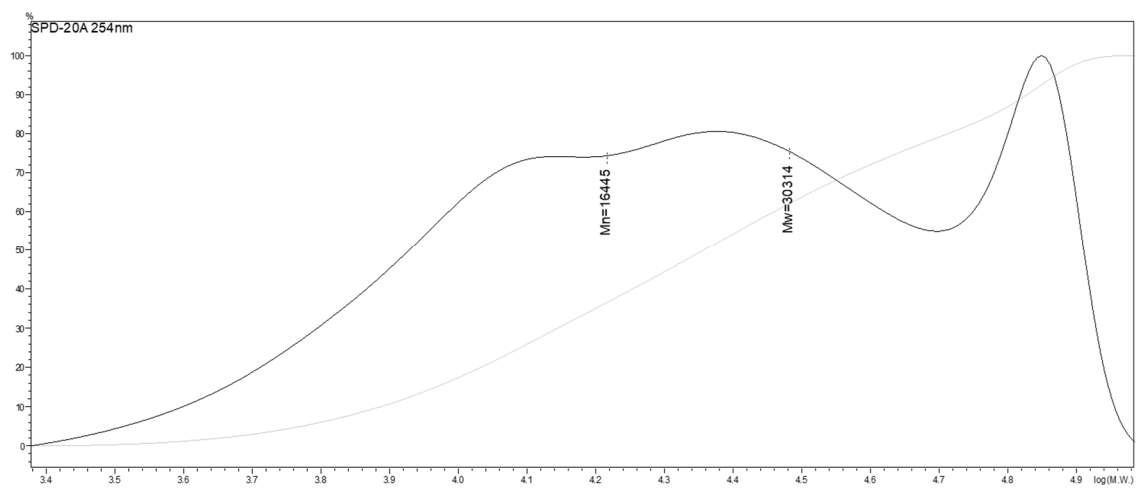
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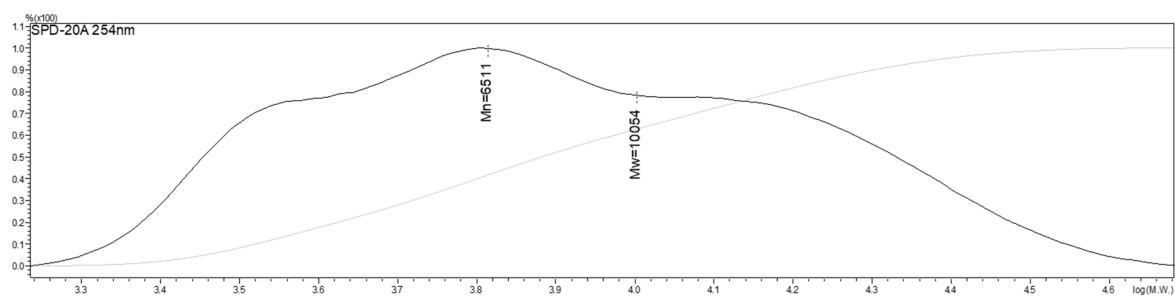
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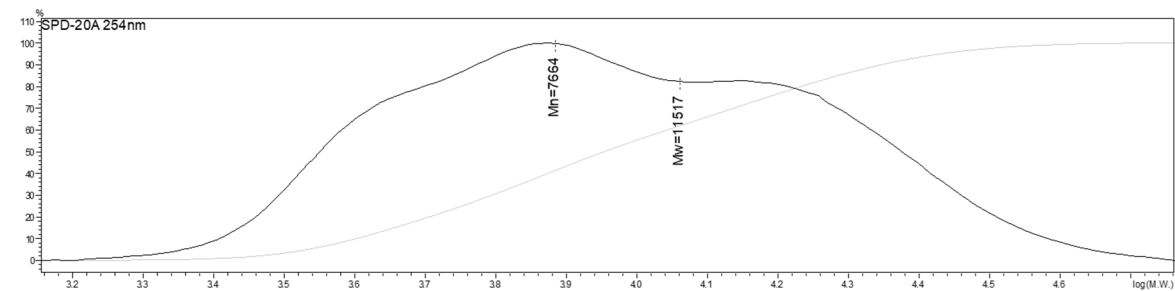
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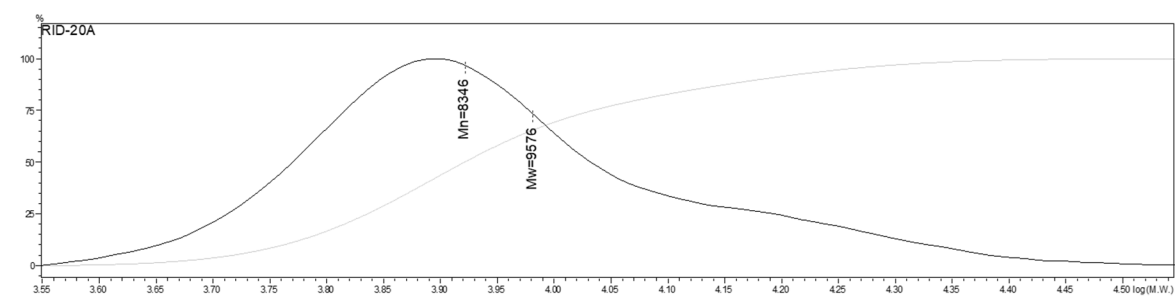
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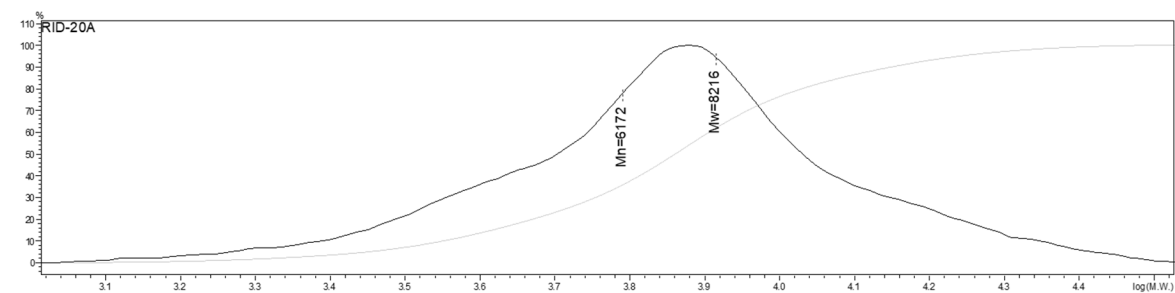
PMBGE – Boc-Gly



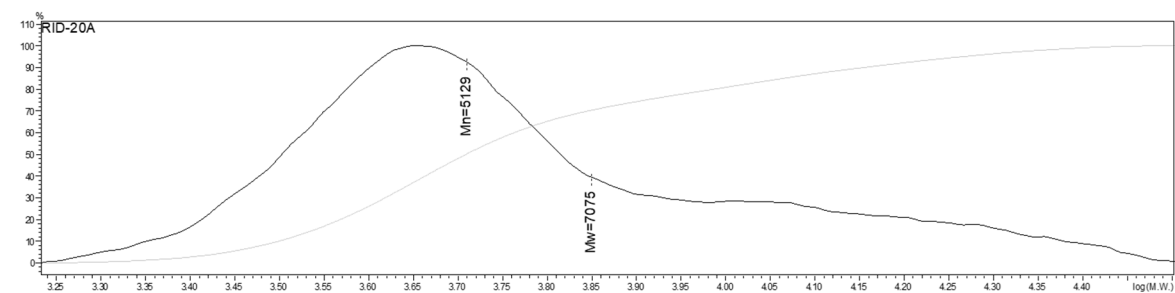
PAGE-co-MAGE (3:1)



PAGE-co-MAGE (1:1)

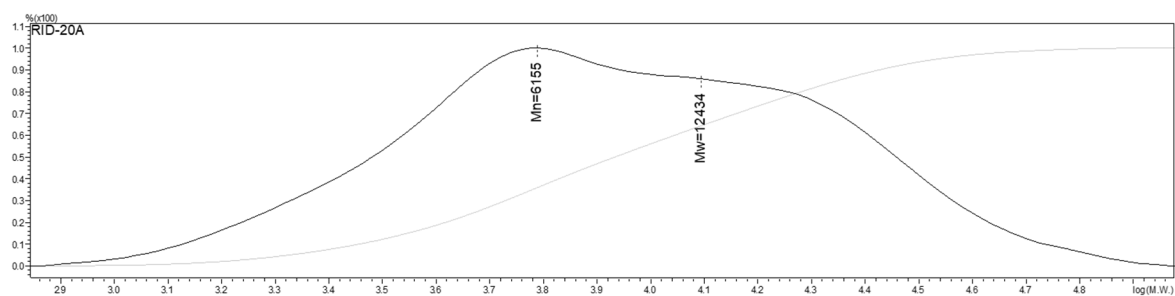


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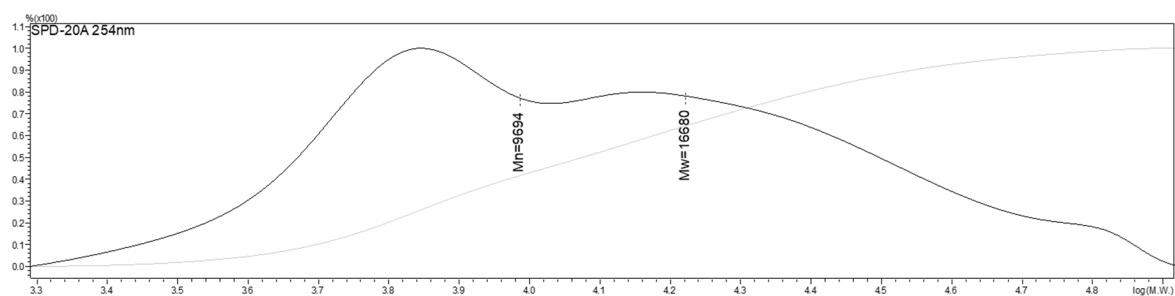
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(3:1)-graft-MA

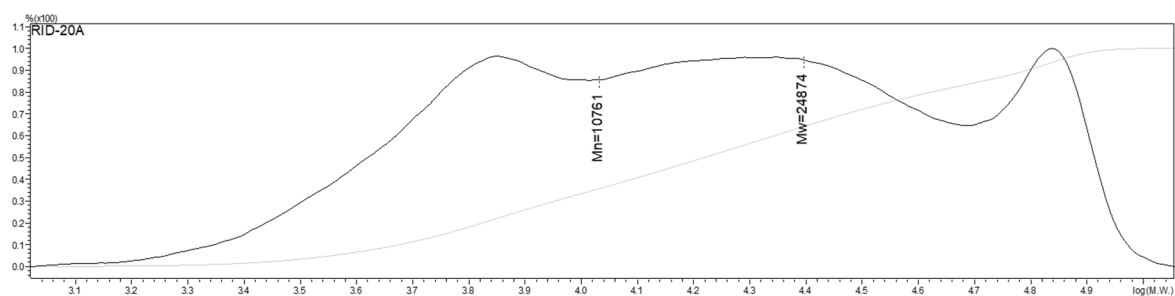


PAGE-co-MAGE

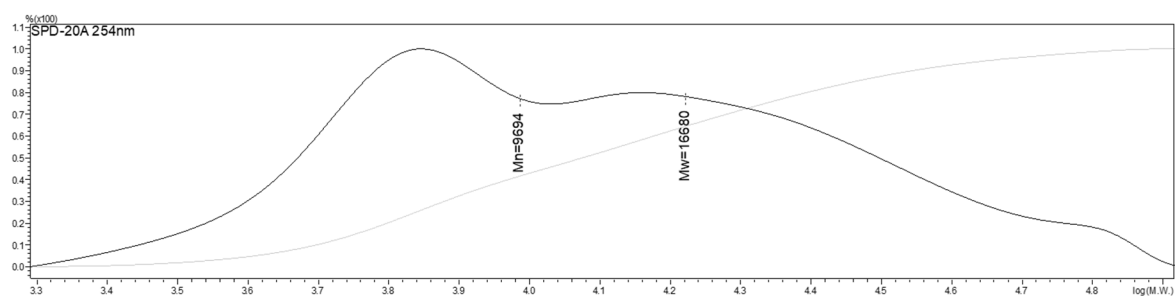
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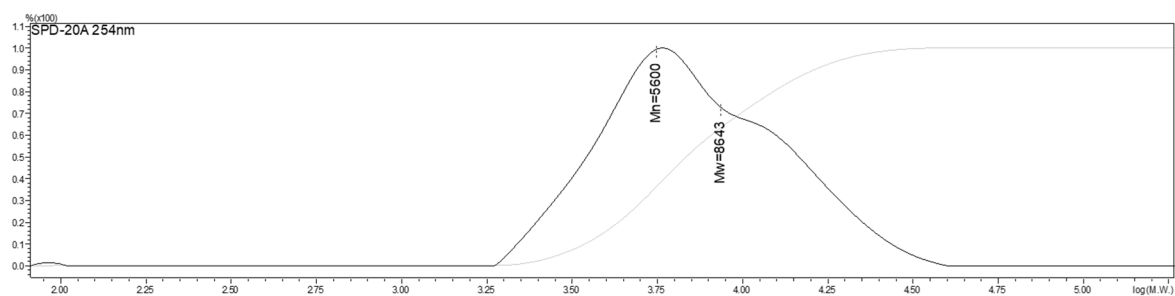
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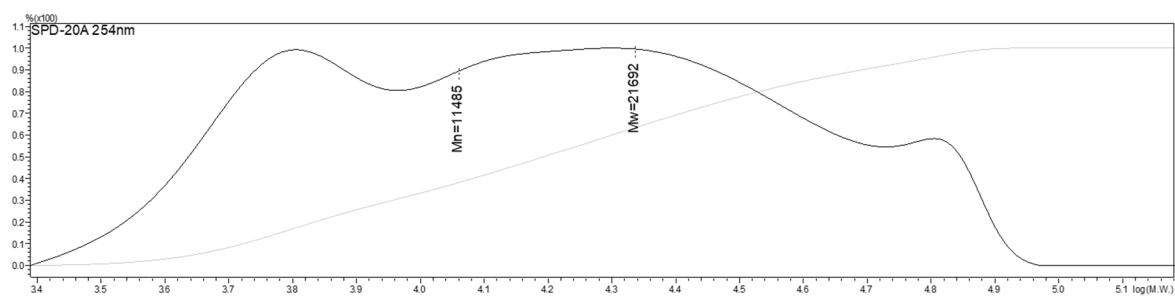
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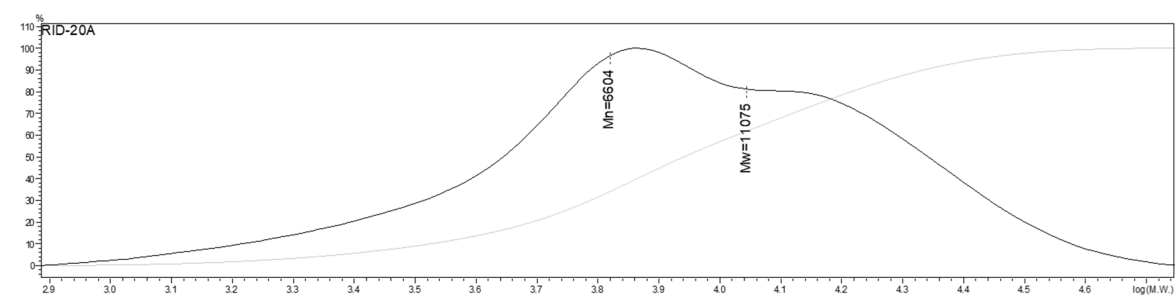
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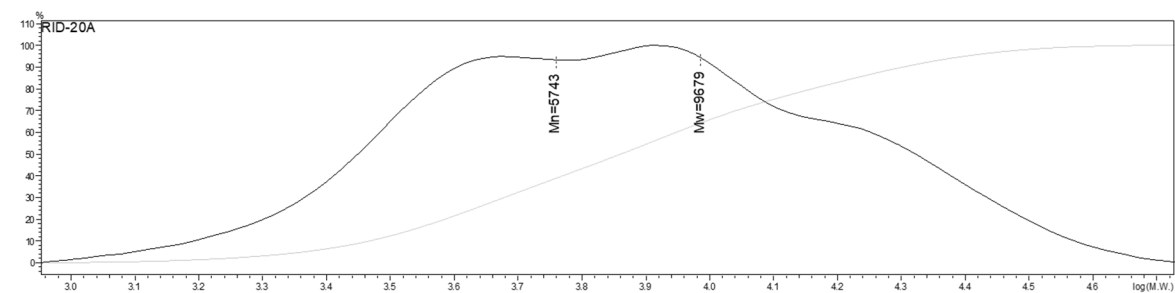
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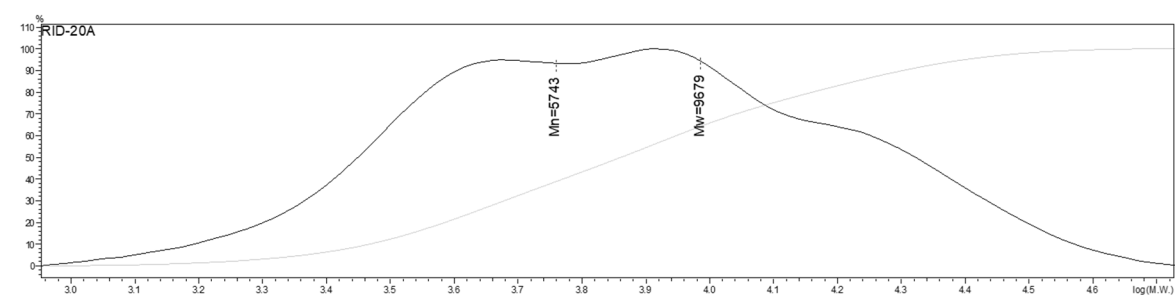
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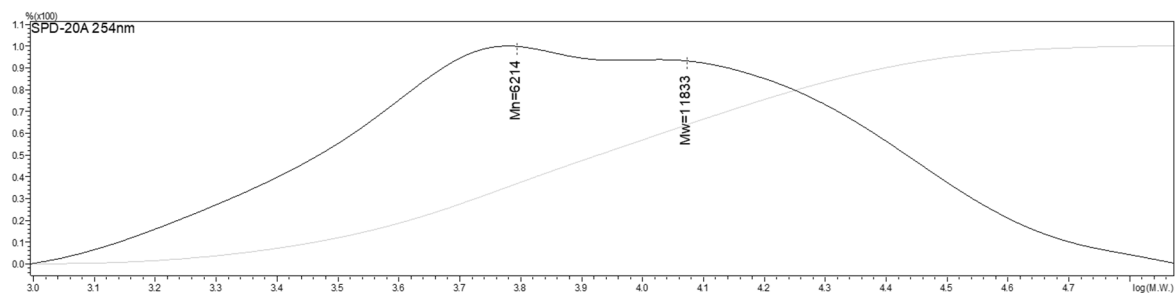
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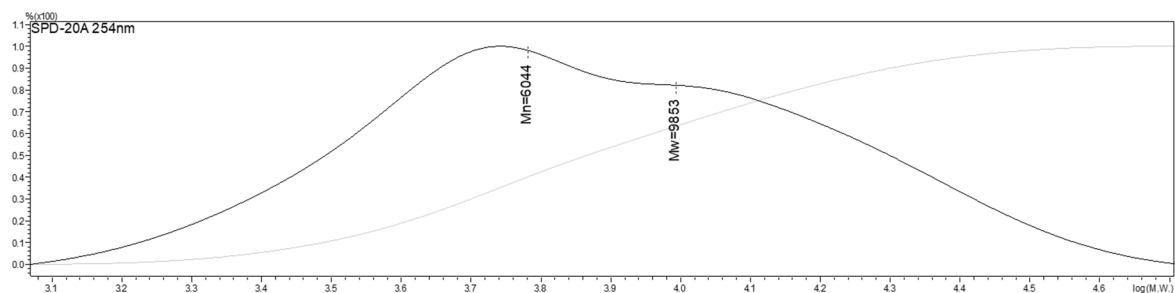
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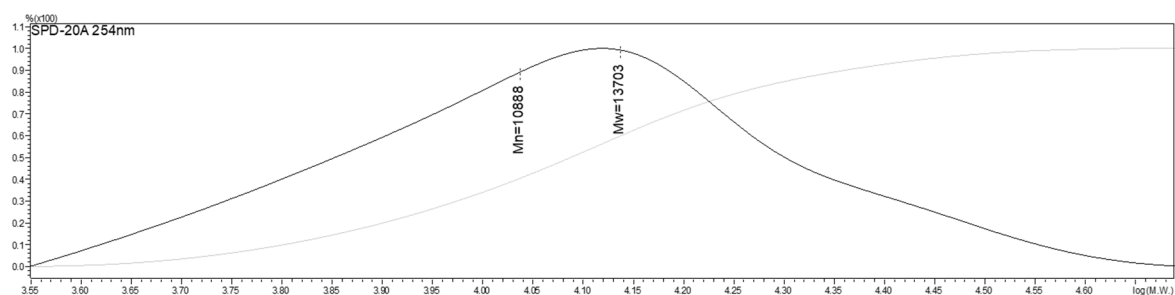
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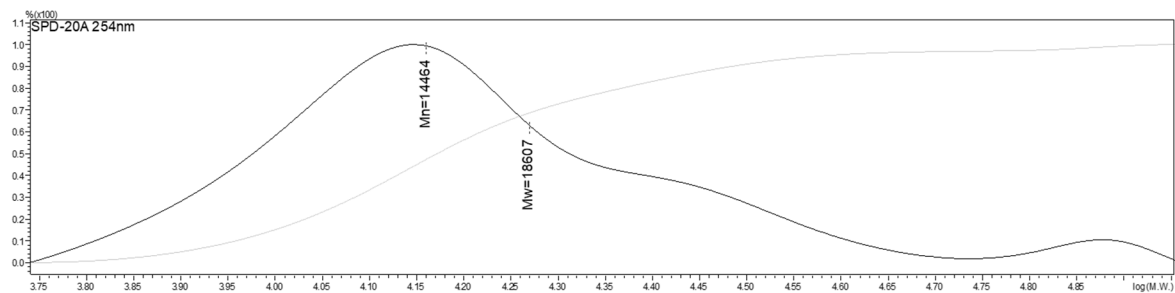
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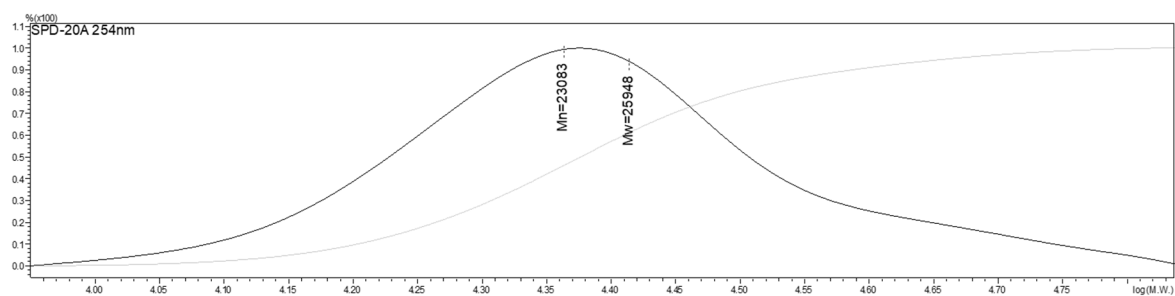
PG-co-PMAGE



PG-co-PMAGE-graft-AA



PMAGE-graft-BMP



PAGE-graft-BMP

